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Volume 239 AUGUST 12, 1948 Number 7

DIAGNOSTIC AND THERAPEUTIC PROBLEMS IN DIVERTICULITIS*

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HARTFORD, CONNECTICUT

DIVERTICULOSIS and diverticulitis are relatively common in persons past the age of forty-five. Ochsner and Bargen[1] discovered that in all the patients registered at the Mayo Clinic in 1933, x-ray study showed diverticulosis in 0.4 per cent, and 7 per cent of all autopsies revealed the presence of diverticula. This corresponds with Morton's[2] figure of 6.5 per cent in 8500 autopsies at the University of Rochester. Among 24,620 cases in which barium enemas were performed Rankin and Brown[3] found diverticulosis in 5.6 per cent.

Diverticulitis occurs at some time in 17 to 27 per cent of all cases of diverticulosis. Rankin and Brown[3] reported the incidence to be about 17 per cent in 1300 cases of diverticulosis, and Abell[4] found it to be 10 to 20 per cent. Ochsner and Bargen[1] observed an incidence of 27 per cent, Smithwick[5] one of 25 per cent, and Willard and Bockus[6] one of 22 per cent.

Most of these analyses of diverticulosis and diverticulitis are concerned with the incidence, etiology and pathological features of the disease. For this reason these aspects are given only brief consideration in the review of the case material that forms the basis of this communication. Emphasis is placed, rather, upon the difficulties of diagnosis that arise from confusion with diseases affecting neighboring organs, and upon the complications.

During the twenty-year period, 1927-1946, 200 cases of diverticulitis were seen at the Hartford Hospital. Of these, 50 were complicated by perforation or obstruction. This incidence is much higher than that in the community at large, because many patients are selected for hospital admission because of symptoms attributable to the complications rather than to the disease itself.

Most of the cases of diverticulitis were seen in persons over forty-five with an antecedent history of spastic constipation or diarrhea. The inflammation in the diverticula was often accompanied by chills and fever, crampy lower abdominal pain with localized soreness, and a recent change in bowel habits. On physical examination, there was almost invariably tenderness in the lower abdomen to the left of the midline, and a palpable, tender mass or muscle spasm was often found. The temperature was elevated in 60 per cent of the cases, and in 36 per cent there was a white-cell count of over 11,000. The erythrocyte sedimentation rate was frequently increased. Diverticula were evident on barium enema, and spasm was usually present. Sigmoidoscopic examination was seldom helpful. The treatment was medical unless complications arose.

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Signs and Symptoms

The diagnosis of diverticulitis was made by the clinical picture in addition to the x-ray findings in 161 cases, at operation in 32, by the clinical picture alone in 5, and at autopsy in 2. Of the 32 patients in whom the diagnosis was made at operation, 15 were suspected primarily to have acute appendicitis, and 17 were operated on with such preoperative diagnoses as pelvic inflammatory disease, acute cholecystitis, intestinal obstruction and ruptured ovarian cyst. In none of the 32 cases was a barium enema performed.

The leading symptoms and signs were similar to those described by other authors and need no comment (Table 1). However, there are two symptoms due to diverticulitis that bear more consideration — back pain and melena.

Pain in the lower back was noted in 20.5 per cent of the cases. Heretofore little emphasis has been placed on this symptom. By applying irritant solutions to the mucosa of the rectosigmoid through a sigmoidoscope, White and Jones[7] demonstrated that pain could be referred from the colon to the lumbosacral region. This radiation of pain is also encountered in mucous colitis and ulcerative colitis, both of which involve essentially the same portion of the sigmoid as diverticulitis. Thus, there is experimental evidence for back pain in lesions of the rectosigmoid. In diverticulitis this symptom is often part of the clinical picture.

Another symptom, often the presenting complaint, is the passage of blood by rectum. This may appear as free blood or as flecks on the fecal material. Melena occurred in 16.5 per cent of the cases, a figure that is consistent with those of other authors (Table 1). Ochsner and Bargen,[1] Smithwick[5] and Morton[2] showed that bleeding occurs in diverticulitis more often than is generally believed. Rankin and Brown[3] found that melena was present in 39 of 142 cases, an incidence of 27 per cent. In discussing Smithwick's[5] paper, C. C. Lund cited a case at the Boston City Hospital in which the chief complaint was severe melena. Soon after admission 1500 cc. of blood was expelled in a bedpan. The patient was operated on as an emergency, and a ruptured diverticulum was found to have involved a large blood vessel, causing extensive intraluminal hemorrhage. In our series, melena was the chief complaint in 6 cases, and in 1 of these the bleeding was extensive enough to require a transfusion.

TABLE 1. *Leading Symptoms and Signs in Cases of Diverticulitis.*

AUTHOR	NO. OF CASES	AVERAGE AGE	SEX RATIO	CONSTIPATION	DIARRHEA	BACK PAIN	MELENA	FEVER	CRAMPY ABDOMINAL PAIN	WHITE-CELL COUNT OVER 11,000
		yr.		%	%	%	%	%	%	%
Ochsner and Bargen[1] ..	151	<50	2.75:1.0	58	26	—	22.0	26	—	—
Morton[2]	111	<45	1.0:1.0	45	37	—	32.0	29	94	29
Smithwick[5]	333	50–60	1.0:1.0	—	—	—	15.7	—	—	—
Willard and Bockus[4] ..	72	55	1.0:1.0	44	15	—	7.0	—	—	—
LeRoyer and White ...	200	60	1.0:1.0	50	31	20.5	16.5	59	80	36

ROENTGENOLOGIC FINDINGS

Spriggs and Marxer[3] pointed out the roentgenologic findings of a prediverticular state that could be recognized before full-blown diverticula had formed. They also described irritability, spasm and narrowing of the lumen as indications of diverticulitis.

Of the 200 Hartford Hospital cases, 161 had barium enemas that showed diverticulosis in the colon, and 133 of these demonstrated definite spasm of the sigmoid, with narrowing of the lumen. The 28 cases of diverticulosis with no spasm had a clinical picture that, with the finding of diverticula by x-ray study, was consistent with the diagnosis of diverticulitis. The X-Ray Department demonstrated a mass by barium enema in 33 of the 161 cases, and the mass was invariably in the sigmoid region. However, the appearance of a mass on x-ray examination is not necessarily diagnostic, since it may be seen with multiple noninflamed diverticula, or it may indicate an unrelated carcinoma or other pathologic process.

DIFFERENTIAL DIAGNOSIS

Whereas diverticulitis is often a clear-cut disease that presents no diagnostic difficulties, there are times when great confusion exists. Smithwick[5] found that an incorrect diagnosis was made in 26 of 64 cases of acute diverticulitis, a 40.5 percentage of error on initial diagnosis. The three conditions most often confused with diverticulitis are appendicitis, carcinoma of the sigmoid colon and masses involving the structures of the genitourinary tract.

Acute appendicitis is often difficult to differentiate from diverticulitis, and in our series 15 patients were operated on with this preoperative diagnosis. In all the appendix was found to be normal, and on exploration an acute, inflammatory diverticulitis of the sigmoid was discovered. In 2 cases the sigmoid loop was to the right of the midline, so that with the findings of crampy abdominal pain, tenderness in the right and middle portions of the abdomen, slight fever and leukocytosis, the diagnosis of acute appendicitis was made. Both patients were found to have normal appendixes.

The following case illustrates the difficulty in differential diagnosis between appendicitis and diverticulitis.

CASE 1. A 68-year-old man had been well until 10 hours before admission, when he suddenly developed a rather sharp, constant pain in the lower back. After several hours the pain worked around to the right lower quadrant. The last bowel movement had occurred several hours before onset of the pain, and the patient vomited three times. His bowel habits had been normal, and there were no urinary symptoms.

The past history was noncontributory.

Physical examination revealed a well developed, well nourished man in moderate abdominal pain. The pertinent findings were confined to the abdomen, where there was persistent spasm, with rebound tenderness in the right lower quadrant and in the midline. Rectal examination revealed slight soreness on the right.

The temperature was 99.6°F. Urinalysis was negative. The white-cell count was 13,000, with 88 per cent neutrophils and 12 per cent lymphocytes.

At operation a normal appendix was found, and further exploration was carried out. In the midsigmoid there was an area of spasm and induration, and several diverticula were seen. Appendectomy was then performed. On the 9th postoperative day a barium enema showed a localized spastic area in the sigmoid, with numerous diverticula.

The only symptom unusual for appendicitis in this case was the initial pain in the lower back, a finding that was present in 20.5 per cent of the 200 cases of diverticulitis.

Carcinoma of the sigmoid is frequently confused with diverticulitis. The clinical diagnosis is often impossible even with the help of barium enemas,

and at operation under observation and palpation it is sometimes very difficult to differentiate the two lesions. The final diagnosis in this type of case usually rests with the pathologist. The association of carcinoma and diverticulitis has evoked considerable discussion in the literature. Rankin and Brown[3] found carcinoma to be present in 4 of 227 cases of diverticulitis. Smithwick[5] encountered the same lesion in 2.9 per cent of 309 cases of diverticulitis. It is now generally believed that the two conditions may exist coincidentally and that carcinoma of the sigmoid rarely, if ever, develops from pre-existing diverticulosis.

Narrowing of the rectosigmoid or evidence of a mass was demonstrated by barium enema in 33 of the 200 cases of diverticulitis under consideration. In none of the 33 could a differential diagnosis be made on the radiographic findings alone. Schatzki[9] states that the differential diagnosis of carcinoma of the sigmoid and diverticulitis by x-ray study is easy in most, difficult in some and impossible in a few cases.

The following case demonstrates the difficulty in differentiating carcinoma of the sigmoid from diverticulitis.

CASE 2. A 67-year-old housewife was admitted to the hospital for cramp-like, lower abdominal and rectal pain of 2 weeks' duration, which was worse during defecation. She also noted bright-red blood with mucus in the stools, and she had moderate tenesmus with a desire to defecate three or four times a day. Her appetite was poor, and she had lost 16 pounds of weight in 2 years. She had had no nausea, vomiting or urinary complaints.

Physical examination showed a well developed but poorly nourished woman who appeared anemic. Tenderness without spasm was noted in the middle-lower portion of the abdomen and in the right lower quadrant. No masses were palpable. Rectal examination was negative. Sigmoidoscopy revealed one small area of discolored bowel just above the third valve, and there was a mass that prevented further observation. No blood was seen.

Examination of the blood disclosed a red-cell count of 3,700,000 with a hemoglobin of 12 gm. and a white-cell count of 10,000. Two stools showed strongly positive benzidine tests. A barium enema was not performed.

On the 11th hospital day the patient was explored with the preoperative diagnosis of carcinoma of the rectosigmoid. The mass that was found in the rectosigmoid was to the right of the midline and seemed to involve the lumen of the bowel. The surgeon believed it was carcinoma. A colostomy was made. Four weeks later, when resection was performed, the mass, which had been obstructing the bowel, was found to be smaller, and several diverticula were encountered. After excision an end-to-end anastomosis was performed. The colostomy was not closed at that time. The specimen consisted of a portion of colon 5.0 cm. in length. There were a few small diverticula lined by normal colonic mucosa, but no evidence of neoplasia was found.

The patient was readmitted 3 months later, and a barium enema revealed no obstruction between the rectum and the colostomy, but showed multiple diverticula and considerable spasm of the sigmoid. At that time the colostomy was closed, and the patient made an uneventful recovery.

This case is significant because of the difficulty in differential diagnosis. Carcinoma was originally considered because the chief complaint was melena. This symptom is more common in acute diverticulitis than has generally been realized. The appearance of the lesion at operation was also misleading. The similarity of such an inflammatory mass to carcinoma on inspection and palpation is so great that not infrequently the final diagnosis rests with the pathologist.

Diverticulitis may be confused with diseases of the lower genitourinary system. The primary complaints may be dysuria, frequency and burning on urination, and the patient may first be studied from a genitourinary point of view. Pressure on the urinary bladder by an inflammatory mass, secondary to an acute or recurrent diverticulitis, accounts for the bladder symptoms (Fig. 1). Such a mass may be found by rectal examination. Extrinsic pressure defects of the urinary bladder may be observed cytoscopically and may be attributed to neoplasm of the rectum or internal genitalia. The following case illustrates the diagnostic confusion that exists when signs and symptoms referable to the bowel and urinary bladder are present.

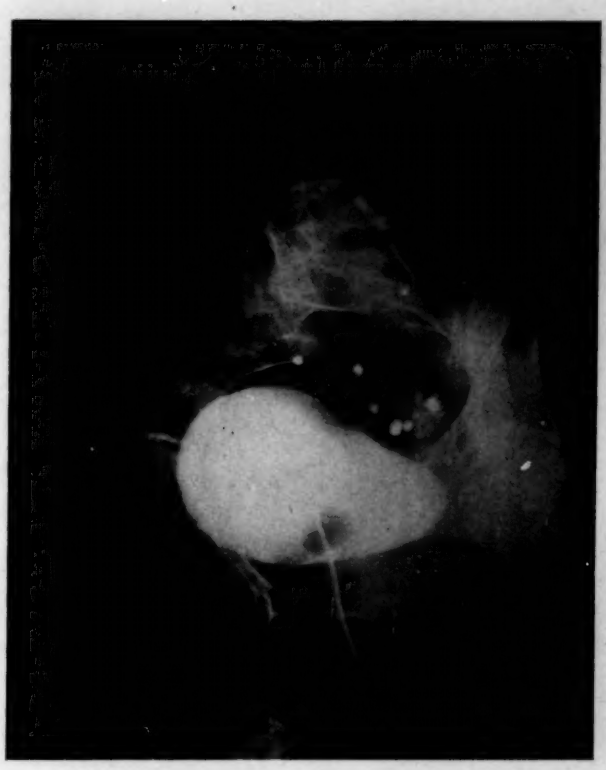

FIGURE 1. *Cystogram Showing a Soft-Tissue Mass Producing Pressure on the Posterior Wall of the Bladder and Rotating It Slightly to the Right.*

The barium-filled diverticula in that region indicate that the mass probably represented an inflammatory diverticulitis.

CASE 3. A 51-year-old office worker had been entirely well until 1 year before admission, when he began to have pain on defecation. At the time of admission it was relatively severe, and he had three to five bowel movements daily, with increasing pain at each successive stool. There had been no diarrhea. Bright-red blood had been present in the stools on several

occasions. In addition, the stools had often been covered by mucus. Recently there had been intermittent, dull, aching lower abdominal pain and urinary frequency.

Physical examination revealed a well developed, slightly thin man in no distress. On rectal examination, there was a firm, rounded mass occupying a position practically in the midline and yet extending well out on each side in the region of the seminal vesicles. It did not suggest a tumor of one or the other seminal vesicles. Distally, it extended down to and was apparently confluent with the prostate.

The temperature, pulse and respirations were normal.

Several urinary specimens were normal, and a culture was negative. The hematocrit was 47 per cent, and the serum protein 6.2 gm. per 100 cc.

On proctoscopy a mass was seen above the prostate. The mucosa of the rectum was intact but puckered down at the junction of the mass with the prostate.

Several needle-punch biopsies were taken. Microscopical examination showed hyalinized strands of fibrous tissue in

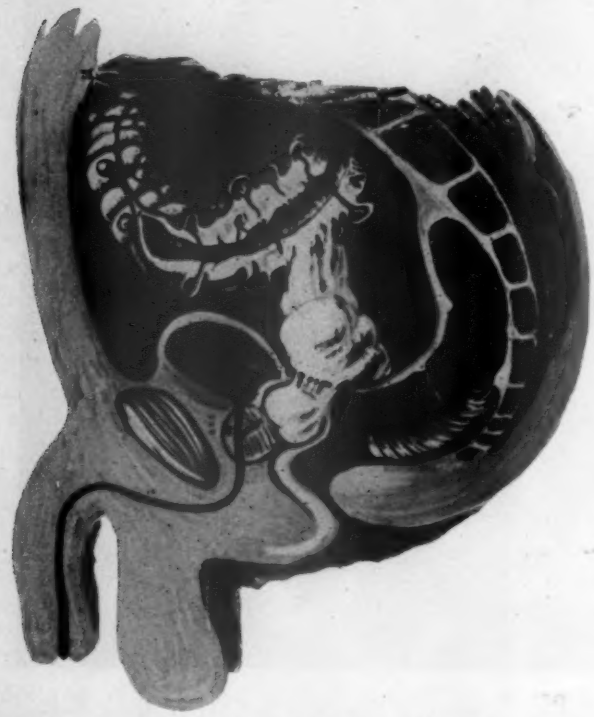

FIGURE 2. *Diagrammatic Sketch of the Findings at Operation in Case 3, Showing a Diverticulitis of the Sigmoid, with a Large Inflammatory Mass.*

A second mass can be seen above the prostate compressing the trigone of the bladder and bulging into the rectum.

which there was a chronic inflammatory reaction. No evidence of a neoplastic process was made out.

On the 4th hospital day, cystoscopy was performed. The trigone was elongated, and the ureteral orifices were farther apart than normal. At a level 1.0 cm. above the orifices, a band of trabeculation was seen, which persisted on distention. The bladder mucosa was normal. X-ray films of the pelvis, after the bladder had been injected with an opaque medium, showed the ureters and the floor of the bladder to be pushed forward. The upper urinary tract was normal.

The patient was explored extraperitoneally through a suprapubic incision. A lemon-sized, inflammatory mass was found in the rectosigmoid attached to the posterior aspect of the bladder. This mass seemed to bulge into the bowel. On palpation, deep in the pelvis, a second mass of equal size was found. This occupied the region of the seminal vesicles and extended distally under the trigone of the bladder to the prostate. Frozen sections proved that this mass surrounded the seminal vesicles and was not primary in them. The primary lesion was in the bowel, and the indurated inflammatory mass was secondary (Fig. 2). A wide resection of the lesion in the sigmoid with an end-to-end anastomosis was carried out. Microscopical study of the sections revealed many diverticula, two of which showed infected sinus tracts into the sigmoid mass. Another section demonstrated that the seminal vesicles were surrounded by chronic inflammatory tissue.

The final diagnosis was diverticulitis of the sigmoid, with secondary seminal vesiculitis.

This case demonstrates how an acute, inflammatory diverticulitis can drain to the rectovesical pouch, with formation of a secondary inflammatory mass closely associated with the internal genitalia and bladder wall.

In the series reviewed, 18 patients with diverticulitis had urinary symptoms, and of these, 3 developed bladder fistulas.

COMPLICATIONS

The complications of diverticulitis are of interest in terms of incidence and of surgical management. Smithwick[5] found that 19.2 per cent of 333 cases of diverticulitis required surgery and that the incidence of such surgical complications in persons over the age of forty was 1:2500.

TABLE 2. *Complications in Cases of Diverticulitis.*

COMPLICATION			No. OF CASES
Perforations:			43
Local abscess		32	
Peritonitis, with ileus		1	
Mechanical obstruction		4	
Fistula formation:		6	
Rectovaginal	3		
Rectovesical	3		
Mechanical obstruction due to local inflammation			7
Total			50

Perforation may lead to localized abscess formation, peritonitis with ileus, mechanical obstruction or fistula formation. These are the most common complications. However, mechanical obstruction due to narrowing of the bowel lumen by a local inflammatory mass may be found in a smaller portion of patients. Twenty-five per cent of the 200 Hartford Hospital cases developed a complication. Local abscesses secondary to perforation were by far the most common (Table 2). Smithwick[5] reported local

TABLE 3. *Location of Abscess in 32 Cases.*

LOCATION		No. OF CASES
Abdominal		18
Pelvic:		14
Rectovesical	9	
Rectovaginal	2	
Colonovesical	1	
Rectosigmoidal	1	
Broad ligament (left)	1	
Total		32

abscesses in 11.9 per cent of 506 cases, with a mortality of 9.3 per cent.

Table 3 indicates the location of the abscesses in the Hartford Hospital series. Of 18 abdominal abscesses, 13 were drained with no further complications. Four led to intestinal obstruction, and 1 resulted in death from generalized peritonitis. However, of 14 pelvic abscesses, 6 developed into fistulas. Three of these drained into the bladder, and 3 into the vagina. The over-all incidence of fistulas was 3 per cent. Morton[2] found 22 cases of fistula formation in 83 complicated cases of diverticulitis. Smithwick[5] records an incidence of 13.1 per cent of spontaneous bladder fistulas in 611 complicated cases. Higgins[10] noted that of 160 cases of vesicocolonic fistula, 57.5 per cent were secondary to diverticulitis.

Mechanical obstruction in the rectosigmoid by an inflammatory mass due to diverticulitis occurred in 7 cases, an incidence of 3.5 per cent. All patients recovered after operation.

TABLE 4. *Types of Operations on Patients with Diverticulitis.*

OPERATION	NO. OF CASES
Diagnostic:	
Appendectomy	15
Laparotomy (only)	3
Hysterectomy	1
Incidental:	
Herniorrhaphy (ventral)	1
Cholecystectomy	2
Posterior gastroenterostomy	2
Hemorrhoidectomy	1
Therapeutic:	
Irrigation and drainage of abdominal (or pelvic) abscess	15
Colostomy	4
Cecostomy	7
Mikulicz (stages I and II)	5
Colostomy, with resection	2
Resection, with anastomosis	5
Total	63

Table 4 indicates that among the 200 Hartford Hospital cases 63 operations were carried out, 19 of them for diagnostic purposes. In all there was acute diverticulitis of the sigmoid. Six patients were operated on for other conditions (Table 4), and acute diverticulitis was found incidentally. Thirty-eight surgical procedures were carried out.

DISCUSSION

Most of the findings of this review of 200 cases of diverticulitis are in accord with those of other authors. From the diagnostic point of view two features are striking: the relatively high incidence of back pain and the frequency of bleeding from the rectum. The latter is somewhat disconcerting, because it detracts from the significance of blood in the rectosigmoid as an indication of polyps or other neoplastic lesions, and complicates the differential diagnosis.

The 25 per cent incidence of perforations and inflammatory obstructions is undoubtedly much higher than that in the community at large, because such complications serve as indications for admission to a hospital. Among 18 patients with abscesses within the peritoneal cavity, there was 1 with generalized peritonitis, and 4 others had intestinal obstruction secondary to localized inflammation. On the other hand, among 14 patients with abscesses in the pelvis, fistulas were encountered in 6. Hence, it appears that inflammatory masses within the peritoneum often lead to intestinal obstruction, whereas those in the pelvis frequently result in fistulas.

SUMMARY

The clinical features of 200 cases of diverticulitis treated at the Hartford Hospital between 1927 and 1946 are reviewed.

The relative incidence of the leading symptoms and signs was essentially similar to those generally reported. A notable exception was the occurrence of pain in the lower back as a prominent feature in 20.5 per cent of the cases. A finding in accord with other authors' experiences, but worthy of special emphasis, was the presence of melena in 16.5 per cent.

Diagnostic confusion occurred most frequently in cases that presented signs suggestive of acute appendicitis, and in those in which masses in the lower abdomen or pelvis could not be differentiated clinically from carcinoma of the bowel or from genitourinary lesions such as ruptured ovarian cyst and carcinoma of the seminal vesicles or prostate.

Complications were encountered in 50 cases, or 25 per cent. These included 7 of obstruction secondary to ligneous induration of the affected sigmoid and 43 perforations. Thirty-two of the latter led to local abscesses, 6 to fistulas, 4 to mechanical obstruction, and only 1 to generalized peritonitis.

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RELAPSING KALA-AZAR*

Report of a Case with Cure Effected by Stilbamidine

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THERE have been many reports concerning the increased incidence of certain tropical diseases in the United States during the postwar period. Service personnel were exposed to and contracted more tropical diseases than any previous group of citizens. There were many cases of dysentery, malaria and dengue among the armed forces. However, the incidence of more exotic tropical diseases, such as leishmaniasis, relapsing fever, cholera and trypanosomiasis, was fortunately much less.

During the immediate postwar period, it became apparent that no widespread outbreaks of tropical diseases in this country would occur chiefly because of the climate, housing and sanitation and the absence of certain vectors. Relapsing and delayed primary attacks of malaria have not been uncommon, and there is no doubt that amebiasis is more evident. Other tropical diseases may be seen sporadically, not only because of a residual focus in returned veterans but also because of increased air travel.

Kala-azar may be encountered. On the basis of a preliminary account of Army medical records, approximately 56 cases of visceral leishmaniasis were reported among Army troops during the period 1942-1945. The diagnosis should be considered in every obscure illness since the over-all untreated mortality throughout the world is 95 and the treated mortality less than 5 per cent. A recent review of the disease in the United States by Ecker and Lubitz[1] emphasizes that kala-azar demands a higher index of suspicion among physicians in the United States.

The clinical picture and course of kala-azar are usually typical. The disease is characterized by an irregular fever, chronicity, splenomegaly, emaciation, anemia and leukopenia. However, the disease may be quite mild and vague. Armstrong[2] has shown that patients may be ill with kala-azar and still have very few obvious complaints. The clinical course varies with the geographic origin of the disease. We have found the disease acquired in the Sudan to be most severe.

The diagnosis of kala-azar is sometimes very difficult. The history and physical examination may be typical, but the demonstration of the causative organism, *Leishmania donovani*, is necessary for diagnosis. Packchanian[3] believes that the diagnosis may be made only by culture of *L. donovani* from the blood, bone marrow, spleen or liver. Scovell[11] does not consider a positive culture necessary. We have not found the peripheral blood cultures of much value in establishing the diagnosis in Americans. The material aspirated from the spleen and bone marrow produces 95 per cent of positive smears and cultures.

Other tests, such as those using aldehyde, antimony and distilled water, may be useful. Feldman[4] has found the formol-gel test of help in suggesting the diagnosis. As this test is based upon the hyperglobulinemia present in kala-azar, it is positive in any condition producing hyperglobulinemia. It was negative in the case reported below.

Antimony preparations, especially neostibosan and urea-stibamine, are the present drugs of choice for therapy. The response to treatment, like the severity, depends on the geographic origin of the disease. Burchenal and Woods[5] reported 3 cases acquired in the Mediterranean area, 2 of which responded poorly to the antimonials. The patients of Waud and Kruger[6] responded to a relatively small amount of antimony. However, their follow-up study was probably of too short duration to meet the criteria for cure of visceral leishmaniasis brought out in a recent review by Marple.[7] It should be emphasized that these patients cannot be considered cured unless they are followed for a minimum of six months.

Hargreaves[8] reported several cases from Italy and Sicily that did not respond to antimony and were treated with urea-stibamine and stilbamidine. His results were satisfactory in the treatment of all cases of Indian and Mediterranean kala-azar. May and Baker,[9] of London, recommend pentamidine for the treatment of patients who relapse after antimonial therapy. It is possible that some kala-azar patients develop resistance to all forms of chemotherapy. In a case recently published, which was complicated by severe anemia and finally cured by splenectomy, the patient received large amounts of antimonials and stilbamidine over a period of two years with only temporary improvement.[10]

Stilbamidine was first brought into clinical prominence by the work of Napier and Sen Gupta[11] at the London School of Tropical Medicine in an effort to find a drug that would cure antimony-resistant kala-azar. It became apparent that all patients not

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responding to antimony therapy were cured with stilbamidine.

The administration of stilbamidine presents several problems, and a detailed discussion is therefore presented. The di-isethionate form of the drug is more soluble and easier to prepare. A maximum of 1.5 mg. per pound of body weight is given in any one day. The entire dose should be mixed with approximately 250 cc. of physiologic saline solution or distilled water to prevent thrombosis of veins. An initial dose of 40 mg. is given to each patient, and this is followed every day with a higher dose until the maximum dose has been attained. A fresh preparation of the solution should be made daily, and it should be given intravenously. Oastler and Fidler[12] demonstrated that stilbamidine is much more hepatotoxic and nephrotoxic in dogs when exposed to light prior to administration. A fresh preparation prevents the occurrence of liver damage sometimes noted in patients. A total dose of approximately 4 gm. is considered adequate. Napier and Sen Gupta[11] administered as little as 1.5 gm. to patients with kala-azar who had previously relapsed after treatment with antimony.

Patients seem to tolerate stilbamidine well, but a few toxic vasomotor manifestations should be mentioned. Various subjective symptoms, usually of a transient nature, include flushing of the face, giddiness, breathlessness, faintness, nausea, vomiting, epigastric discomfort, salivation, sweating, tachycardia and occasionally collapse. After the first few injections of the drug there is usually a fall in blood pressure, which is frequently marked. As the blood pressure returns to its normal level, most of the symptoms disappear, usually within half an hour or so. These reactions may be controlled or prevented by an injection of epinephrine.

Nervous symptoms, including paresthesia, peripheral neuritis, paraplegia and trigeminal neuropathy, may develop after treatment has been continued for some time, suggesting a cumulative action. The most important of these is an unexplained bilateral trigeminal neuropathy in which light touch is absent and pain and temperature sensation is preserved along the course of the fifth cranial nerve. Numbness and tingling over this entire area may be a real complaint. This symptom complex generally begins three or four months after administration has been completed and may last for several years.

The following case is presented because of several interesting features in diagnosis and treatment. The patient had malaria and amebiasis in addition to kala-azar and presented an apparent cure when treated with quinine, quinacrine (atabrine) and emetine. One sternal-marrow puncture was negative, and the *L. donovani* bodies were found on only two of the nine slides made from the second puncture. Two courses of neostibosan failed to cure the infection. One course of stilbamidine was successful.

Case Report

A 36-year-old former Army officer was overseas in India, upper Assam and China from March, 1944, to November, 1945. In August, 1944, he had an acute attack of tertian malaria treated with quinine and atabrine. Intermittent diarrhea was present and was occasionally treated with small amounts of sulfaguanidine and diodoquin.

The patient felt well on his return to the United States until the onset of his present illness on March 3, 1946. This was characterized by chilliness, fever, sweats and malaise. He was first seen on March 6, when the temperature was 102°F., the spleen was palpable three fingerbreadths below the costal margin and the liver was tender, its edge being palpable two fingerbreadths below the costal margin. A blood smear revealed *Plasmodium vivax*. Atabrine therapy was followed by an apparent response. Quinine sulfate (0.6 gm. daily) was prescribed as a maintenance dose.

On March 25 the patient reported a recurrence of malaise, chilliness, fever and sweats and was confined to bed at home. His temperature fluctuated widely, readings of 104 and 105°F. being reported and the minimum being 99°F. Drenching sweats were prominent, and insomnia was troublesome. There was no frank chill. An increased looseness and frequency of stools was noted, which continued for several weeks. At times, the patient was incontinent. A pasty type of pallor was present.

The spleen was hard and palpable three or four fingerbreadths below the costal margin. The liver edge was palpable two fingerbreadths below the costal margin and was tender and sharp. On March 28 examination of the blood disclosed a red-cell count of 4,090,000, with a hemoglobin of 11.5 gm. (76 per cent), and a white-cell count of 3700, with 49 per cent neutrophils, 10 per cent band forms, 39 per cent lymphocytes and 12 per cent monocytes. Malaria smears were negative. Urinalysis was negative. Quinine sulfate (0.6 gm. three times a day) was administered from March 25 to 29, with no response objectively or subjectively.

On March 29 the patient was admitted to a hospital. His course was stormy. Chills, fever, vomiting, diarrhea, drenching sweats, apprehension and disorientation were prominent. His temperature had a tendency to double daily spikes. Six to eight liquid stools occurred daily. Vomiting occurred two or three times daily. The physical findings remained the same. The patient began to look emaciated. The results of laboratory studies performed from March 30 to April 2 are presented

Table 1. *Pertinent Laboratory Data.**

Date	Red-Cell Count	Hemoglobin	White-Cell Count	Neutrophils	Lymphocytes	Monocytes	Eosinophils	Blood Culture	Stool Examination
1946	*x10⁶*	*gm./100 cc.*	*x10³*	%	%	%	%	*at 48 hr.*	
March 30.....	3.50	11 (67%)	3.8	58	40	4	0	—	—
March 31.....	—	—	—	—	—	—	—	No growth	—
April 1.....	3.35	10 (60%)	3.5	62	33	3	2	—	Negative
April 2	—	—	—	—	—	—	—	No growth†	Negative
Apr 13	—	—	—	—	—	—	—	—	Cysts of *Endamoeba histolytica*

*Agglutinations for *Eberthella typhosa* (strains A and B) *Proteus vulgaris* (strains OX2 and OX19) and *Brucella abortus* were negative in all dilutions on March 31.

†Penicillinase added.

in Table 1. Urinalysis was negative. A sternal puncture on April 3 was negative for *L. donovani*. Specific treatment with atabrine (1.2 gm.) and penicillin (640,000 units), in addition to supportive measures, was ineffective.

He was transferred to Walter Reed General Hospital on April 4. The white-cell count was 2100, with 60 per cent neutrophils, 38 per cent lymphocytes and 2 per cent monocytes. The total protein was 5.75 gm. per 100 cc., with an albumin of 3.8 and a globulin of 1.95 gm. per 100 cc. A blood culture, complement-fixation test for amebiasis, Widal test on the stools and stool culture were negative, as was the formol-gel test.

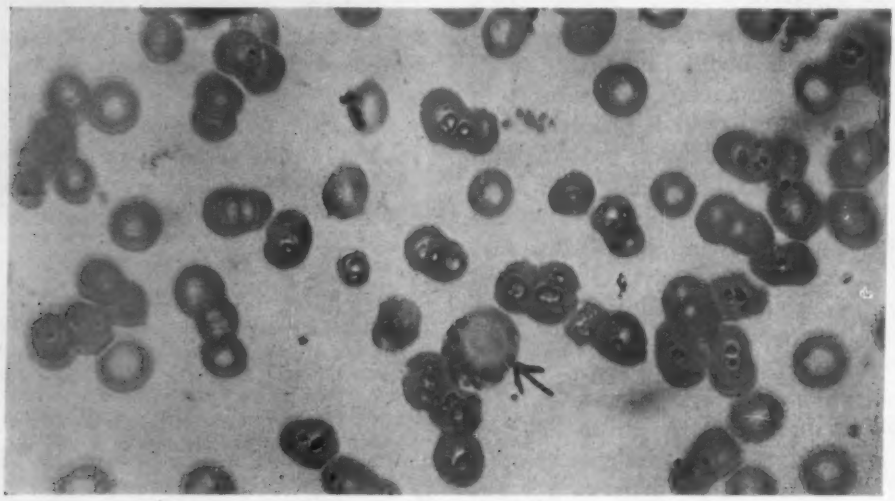

FIGURE 1. *Endothelial Cell Containing Leishman-Donovan Bodies (Arrow). The dark objects within the red cells are artefacts.*

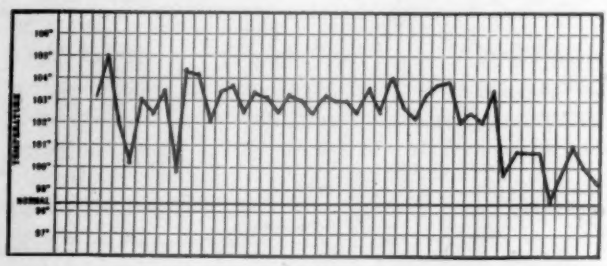

FIGURE 2. *Temperature from March 29 to April 5.*

The differential diagnoses were amebic hepatitis, visceral leishmaniasis and typhoid fever. Because cysts of *E. histolytica* were found in the stools and the liver was enlarged and tender, a course of emetine, (0.55 gm.) was administered. A dramatic response to emetine was noted. The temperature dropped to normal levels, and the appetite improved; the red-cell count rose to 4,000,000, and the white-cell count to 5000. The patient felt well. He was discharged on April 14, and he continued to improve. The size and tenderness of the liver decreased, but the spleen remained the same size.

This apparent cure continued for approximately 2 weeks, when he began running a low-grade fever, which gradually increased. Malaise recurred, and he was readmitted to Walter Reed General Hospital on May 1 for further treatment of what was thought to be an amebic abscess. The entire picture was identical with that during the previous episode with splenomegaly, hepatomegaly and the following laboratory studies: negative malarial smears, a red-cell count of 2,440,000, with a hemoglobin of 43 per cent, and a white-cell count of 2750, with 59 per cent neutrophils, 38 per cent lymphocytes, and 2 per cent monocytes. The total protein was 5.65 gm. per 100 cc., with an albumin of 3.91 and a globulin of 1.74 gm. The formol-gel test was negative. An x-ray film of the chest was normal.

The patient failed to respond to emetine, and his temperature rose to 104°F. It was believed that he had either an abscess of the liver that was not responding to emetine or kala-azar, which had not been proved. Fluoroscopic study of the right leaf of the diaphragm demonstrated good mobility on inspiration and expiration. The white-cell count remained low. In view of these findings, abscess of the liver or diffuse amebic hepatitis was deemed unlikely. A repeated sternal puncture revealed *L. donovani* organisms on two of nine smears, and a culture of the aspirated blood from the sternal marrow was later reported positive for *L. donovani* (Fig. 1). This confirmed the diagnosis of kala-azar. A good response was brought about with a total of 2.7 gm. of neostibosan, and he was discharged on May 20, afebrile and well. The red-cell count was 3,830,000, with a hemoglobin of 60 per cent, and the white-cell count was 5250.

The patient was followed during the months of June and July periodically. Toward the beginning of July, it was apparent that he was not cured of his disease. Although he ate well and led a restful life, he did not fully regain his strength. His color was pasty. His liver and spleen continued to be palpable. The hemoglobin and red-cell count dropped from 85 per cent and 4,390,000 on June 27 to 70 per cent and 3,580,000 on July 10. It was believed that another course of neostibosan should be instituted. This was carried out — from July 15 through 26. He received a total of 3.45 gm. of neostibosan at home with apparent complete remission. There was a reduction in the size of the liver and spleen, although they still remained palpable.

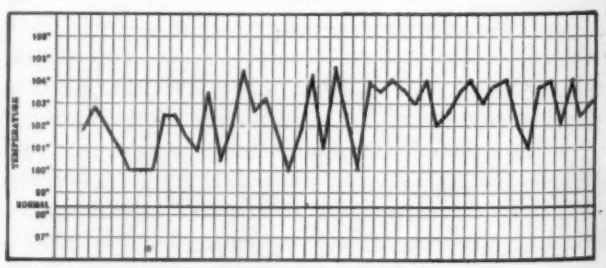

FIGURE 3. *Temperature from May 1 to May 8.*

After 1 month of apparent cure, a recurrence of fever and malaise began on August 24. This continued, and he was

admitted for the third time to Walter Reed General Hospital on August 30, remaining until September 20.

On admission it was evident that the patient was markedly anemic. The temperature was 101°F.; the spleen was palpated three fingerbreadths below the left costal margin on deep inspiration (one and a half fingerbreadths at rest) but was not tender. The liver was not palpable.

On August 31 examination of the blood revealed a red-cell count of 2,100,000, with a hemoglobin of 46 per cent, and a white-cell count of 3100, with 36 per cent lymphocytes, 6 per cent monocytes, 3 per cent basophils and 55 per cent neutrophils.

On September 20 the red-cell count was 3,750,000, with a hemoglobin of 78 per cent, and the white-cell count 6300, with 45 per cent neutrophils, 49 per cent lymphocytes, 4 per cent monocytes, 2 per cent eosinophils and 0.8 per cent reticulocytes. Urinalysis was negative. The total protein was 7.8 gm. per 100 cc., with an albumin-globulin ratio of 1.4:1.

Stilbamidine therapy was instituted, consisting of 150 mg. per day intravenously for the first 2 weeks and 300 mg. daily for the last week, a total of 4.325 gm. being given in the 21-day period. The temperature reached normal levels on the 12th day of therapy and has continued so to date. The edge of the spleen was palpated five fingerbreadths below the left costal margin during the first 2 weeks of therapy and gradually receded. On the 21st day of therapy, the spleen extended only one and a half fingerbreadths below the costal margin on inspiration, and the edge was barely palpable at rest.

The temperature curves during the hospital admissions are demonstrated in Fig. 2-5.

After his discharge from Walter Reed General Hospital on September 20, the patient continued to feel well. He regained his strength and carried on his normal activities. On October 16 the liver edge was not felt and the tip of his spleen was just barely palpable. On January 15, 1947, he noticed a numbness of his upper lip, both cheeks, ears and temples. There was definite anesthesia to light touch, but no change in pain or temperature sensation. Motor components were unchanged. This was thought to be dissociated anesthesia of the fifth cranial nerve.

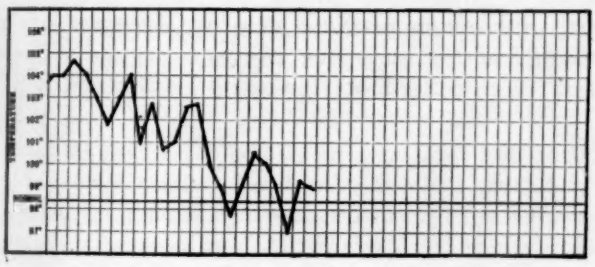

FIGURE 4. *Temperature from May 9 to May 12.*

On February 24 the hemoglobin was 91 per cent, the red-cell count 4,470,000, and the white-cell count 6250, and the patient reported improvement in the neurologic sensations.

On June 15, there was continued improvement in the neurologic symptoms. There had been no recurrence of fever or malaise, although the tip of the spleen was still palpable.

SUMMARY

A case of kala-azar is reported. Difficulties in diagnosis were encountered, emphasizing the varied nature of the disease. The patient relapsed after two courses of neostibosan. Complete cure was obtained with 4.325 gm. of stilbamidine. It is suggested that kala-azar be included in the differential diagnosis of any obscure febrile illness. Stilbamidine may be considered efficacious in relapsing visceral leishmaniasis until less toxic drugs have been proved to be of value.

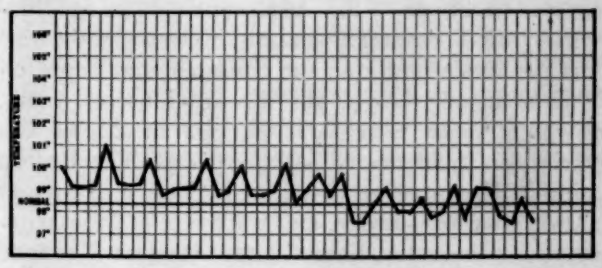

FIGURE 5. *Temperature from August 31 to September 5.*

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CESAREAN SECTION AT THE BOSTON CITY HOSPITAL, 1936-1946*

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BOSTON

AT THE Boston City Hospital in the ten-year period from 1936 to 1946 there were 961 cesarean sections — 3.3 per cent of 28,341 deliveries, or 1 cesarean section in every 29 cases. This incidence is about the same as that reported by Duncan and Doyle[1] for the previous ten years, in which there were 703 sections in 22,880 deliveries, an incidence of 3.07 per cent. The Boston Lying-in Hospital[2] reported an incidence of 3.4 per cent on its ward service, and the State of Massachusetts 3.3 per cent.[3] These figures suggest a general attitude of conservatism throughout Massachusetts in the performance of cesarean section, especially in the larger public ward service in the city of Boston.

From 1936 to 1939 there was a steady increase in the percentage of cesarean sections (Table 1),

TABLE 1. *Yearly Incidence of Cesarean Section.*

YEAR	NO. OF DELIVERIES	NO. OF CESAREAN SECTIONS	INCIDENCE
			%
1936	3180	84	3.5
1937	3295	135	4.0
1938	3320	142	4.2
1939	3262	88	2.7
1940	3225	83	2.5
1941	2969	91	3.0
1942	2918	81	2.7
1943	2447	96	3.9
1944	1964	82	4.1
1945	1761	79	4.5

which gave way to an abrupt decline in 1939, when x-ray pelvimetry was adopted as an additional check on a patient's ability to deliver through the natural channels. Since 1943 surgeons have been more radical in the choice of abdominal delivery under the protecting influence of the blood bank, the sulfonamides and penicillin. The present tendency seems everywhere to be a broadening of the indications for the cesarean operation.

AGE

Patients thirty-five years of age and over, called injudiciously "the elderly group," comprised 70 per cent of the series. These patients suffer more of the complications requiring cesarean section, and protection of the baby of the elderly primigravida provokes more serious consideration than that of the younger gravida with a longer span of reproductive years ahead of her. In addition, prolonged labor and difficult forceps deliveries seem to cause in the former group more chronic debilitating conditions, such as prolapse, cystocele and relaxations of the pelvic floor.

PARITY

Twenty-eight per cent of the sections were done on primigravidas. In the remaining 72 per cent constituting the multiparous cases, 606, or 87 per cent of 689 cases, were repeat sections. Only 83 cases (8 per cent of the total series) of primary cesarean section were done on multiparas.

The extraordinary number of repetitions of abdominal hysterotomy (Table 2) is due to the fact that no sterilizations are done at the Boston City Hospital, nor is a Porro cesarean hysterectomy done unless there is definite uterine disease to warrant its adoption. It is interesting that there were only 6 ruptured uteri in the decade of this study, 2 traumatic and 4 occurring in patients with scars from previous cesarean sections, all of whom had had only one previous section. There were no ruptured uterine scars in the 602 other repeat sections, in 257 of which the patients were experiencing abdominal delivery for the third time or more frequently.

TABLE 2. *Primary and Repeat Cesarean Sections.*

TYPE OF SECTION	NO. OF CASES
First	355
Second	349
Third	181
Fourth	52
Fifth	16
Sixth	7
Seventh	1

INDICATIONS

The indications for cesarean section are presented in Table 3. If a patient has had a section on her first delivery she is invariably treated in like manner in subsequent pregnancies. On the other hand, if she has had a vaginal delivery without difficulty prior to her first section and there was no sepsis after the cesarean section, she is given a test of labor under careful observation. If the cervix yields readily and there is no evidence of dystocia, delivery is effected through the natural route as soon as full dilatation is attained. If a patient has

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had more than one cesarean section she is not allowed to go into labor, but a repeat section is done within the last four weeks of pregnancy as soon as the estimated size of the fetus offers fair assurance that the baby will weigh approximately 5 pounds or over.

The abdominal deliveries for disproportion since 1939 were done only after x-ray pelvimetry demonstrated inadequacies in the size and shape of the pelvis and then only after a fair test of labor. In this clinic the incidence of disproportion requiring cesarean section is about 1 in 100 cases.[4]

Uterine inertia, which seems to be interrelated with cervical dystocia, accounted for 36 of the operations. In these most disconcerting cases there is no discrepancy between the fetal head size and that of the pelvis and yet the uterine contractions and the rigidity of the cervix fail to allow natural termination of labor. Contraction-ring dystocia may rightfully be included in cervical dystocia, making a total of 40 cases, or 4 per cent of the cesarean sections being done for abnormalities in the propulsive factors of labor. This, we believe, is a comparatively low incidence.

Primiparous breech delivery was the causative factor in only 1.5 per cent of the cases. Of 1200 breech presentations only 17 cases, all in primiparas, required cesarean section. X-ray pelvimetry is done routinely in all cases of primiparous breech delivery, and an adequate test of labor allowed before the decision is made to perform an abdominal delivery.

Previous gynecologic plastic operations accounted for but 2 cases of the series. The rarity of this indication is due to the conservative policy of performing extensive vaginal repairs until the patient has passed the child-bearing age.

Placenta previa, we believe, is best treated by cesarean section, except in cases of low implantation with slight bleeding and a cervix effaced and dilatable, assuring a speedy onset and rapid termination of labor after artificial rupture of the membranes. Patients with placenta previa, if the diagnosis is made with sufficient confidence from soft-tissue x-ray films and cystograms, may undergo cesarean section without corroborative vaginal examination. If the x-ray film does not offer enough proof of the abnormally situated placenta a sterile vaginal examination is done as near term as possible with the operating room prepared for abdominal delivery.

Premature separation of the placenta is usually managed with cesarean section after the patient has recovered from the initial shock. In an occasional case with a soft, dilatable cervix rupture of the membranes and a tight abdominal binder are employed.

Fibroids were a rare indication for cesarean section, accounting for only 4 cases in this study, and these presented obstructing tumors to delivery from below. Myomectomy was rarely done with the section, and there were no Porro cesarean hysterectomies with fibroids as an indication.

Sixteen cesarean sections were done for severe toxemia and eclampsia, a low incidence that is due partly to the infrequency of toxemias in the past decade and also to the conservative management of these cases. There were 9 cases of severe pre-eclampsia and 7 of eclampsia in this group with no deaths. One patient with severe toxemia with abruptio placentae, however, died of uremia and cortical necrosis of the kidneys. In the patient with severe toxemia who has reached a quiescent stage and in whom delivery must be effected as expeditiously as possible, if the cervix is not ripe for induction of labor, elective cesarean section is done preferably under local anesthesia with pentothal sodium intravenously, or with pentothal alone.

TABLE 3. *Indications for Cesarean Section.*

INDICATION		No. OF CASES
Repeat		606
Disproportion		141
Uterine inertia		36
Contraction ring		4
Primiparous breech delivery		17
Gynecologic repair		2
Placenta previa		68
Marginal	13	
Partial	23	
Complete	32	
Premature separation of placenta		57
Fibroid uterus		4
Severe toxemia		9
Eclampsia		7
Ruptured uterus		6
Rheumatic heart disease		4

There were 6 cases of ruptured uterus, 2 traumatic from attempted delivery outside the hospital and 4 that followed rupture of scars of previous cesarean sections. The treatment was always hysterectomy.

Four patients with rheumatic heart disease were decompensated at the time of operation and were managed by cesarean section with considerable misgiving and with a fatal outcome in 3 cases. Medical consultation had offered an unfavorable prognosis whatever course was selected and suggested possible amelioration of symptoms if the fetus were removed through the abdominal route with the least possible trauma under local anesthesia. The severely decompensated cardiac patient in the last trimester will always present a difficult problem with a poor prognosis no matter how the pregnancy is terminated.

OPERATORS

Four hundred and forty cases were done by the residents and interns, and 521 by the visiting staff. Paradoxically, there were only 3 deaths among

the cases done by the residents, a mortality of 0.7 per cent, whereas 20 patients who were operated upon by the visiting staff died, a mortality of 4 per cent. The discrepancy in mortality rates is evidence that the more experienced group assumed the responsibility of the poorer risks. However, this fact should not detract appreciably from the excellent record of the resident staff.

Morbidity

The incidence of morbidity is presented in Table 4. A temperature of 100.4°F. or higher on any two days of the puerperium, exclusive of the first twenty-four hours, was considered evidence of infection. The morbidity in the entire series was 26.6 per cent. Since the introduction of the sulfonamide drugs and penicillin this has been reduced to 10 per cent. The rate for elective cesarean section was 15 per cent in contrast to 37 per cent for the emergency operation. The morbidity rate in the few cases in which the Waters extraperitoneal operation was done was 40 per cent. The patients who had suffered considerable blood loss were more inclined to show evidence of infection postoperatively, averaging 45 per cent. Ruptured membranes over twelve hours or labor over twenty-four hours caused temperature elevations in 40 per cent of the cases. Prophylactic administration of penicillin and the sulfonamides in cases potentially infected in which cesarean section is anticipated, together with the liberal use of transfusion to compensate for blood loss, is lowering these figures to a great extent.

Table 4. *Morbidity.*

Duration of Fever	No. of Cases	Incidence
days		%
0	706	73.5
2	98	10.2
3	70	7.3
4	25	2.6
5 or more	62	6.4

Type of Operation

Most of the cesarean sections were done by the low cervical technic, which showed an increase from 79 per cent reported by Duncan and Doyle[1] to 91 per cent in our series (Table 5). The transverse incision was preferred because it was confined more readily to the lower uterine segment and provided less operative difficulty in repeat sections. The classic incision, which waned in popularity from a 20 per cent incidence in the previous decade to 6 per cent, is now performed only when the lower-segment operation is not feasible because of varices, fibroids or inextricable adhesions preventing access to the lower segment.

The Waters extraperitoneal operation was done in 10 frankly infected cases, with no deaths. If patients who may require cesarean section are given prophylactic penicillin and sulfonamide therapy while undergoing a test of labor, the indications for the Waters technic are considerably decreased.

The Porro cesarean hysterectomy was done in 20 cases. Six cases of ruptured uterus were treated in this manner. The other 14 were cases of uncontrollable bleeding, which included 6 cases of placenta previa, 5 of couvelaire uterus following abruptio placentae, 2 of hemorrhage from post-partum uterine atony, and 1 of placenta accreta with the placenta adherent to a previous cesarean scar. There were no deaths from the Porro operation.

Table 5. *Types of Operation.*

Operation		No. of Cases	Incidence
			%
Low cervical		874	91
Transverse (Kerr)	800		82
Longitudinal (Kroenig)	74		8
Classic		57	6
Extraperitoneal (Waters)		10	1
Porro		20	2

Anesthesia

The types of anesthesia are presented in Table 6. Prior to 1941 the anesthetic of choice was nitrous oxide, oxygen and ether. Since 1941 spinal anesthesia has been used almost routinely except in bleeding cases. Sodium pentothal was administered intravenously in 4 cases of severe toxemia. Local anesthesia was employed in only 6 cases, but its use should be adopted more generally since it is the safest of all anesthetics. Anesthesia for cesarean section is now administered only by the qualified men of the anesthesia service.

Table 6. *Types of Anesthesia.*

Anesthesia	No. of Cases
Nitrous oxide, oxygen and ether	532
Open ether	96
Spinal	323
Local	6
Pentothal	4

Fetal Mortality

There were 72 fetal deaths making a gross fetal mortality of 7.5 per cent (Table 7). Discounting the cases of stillbirth due to ruptured uterus and hemor-

rhage, the rate was 3 per cent. Of the neonatal deaths the majority were due to prematurity, especially in the patients with placenta previa. In the cases in which the cesarean section was repeated there were 9 neonatal deaths, a mortality of 1.5 per cent.

Table 7. *Fetal Mortality.*

Cause		No. of Deaths
Stillbirth:		44
Ruptured uterus	6	
Abruptio placentae	20	
Placenta previa	18	
Neonatal death:		28
Prematurity	12	
Atelectasis	10	
Cerebral injury	4	
Erythroblastosis	1	
Congenital abnormality	1	

Maternal Mortality

The causes of death are presented in Table 8. There were 23 maternal deaths, a mortality of 2.4 per cent; this is an improvement over the previous decade, in which the rate was 4.3 per cent. Of these 23 cases, 7 had been badly managed by private physicians, and the patients were in poor condition. These cases included 3 of separated placenta with the patient in shock and badly exsanguinated, 2 of placenta previa in which the patients had been allowed to bleed for a long time before the decision was made to send the patient to the hospital and 2 of cephalopelvic disproportion in which the patients had been in labor over forty-eight hours and in which several attempts at manual dilatation of the cervix and forceps delivery had been made unsuccessfully. The mortality for the cases followed through the entire pregnancy was 1.6 per cent.

Table 8. *Maternal Mortality.*

Cause	No. of Cases	Percentage of Total
Hemorrhage	8	34.8
Peritonitis	4	17.4
Embolism	3	13.0
Anesthesia	3	13.0
Cardiac decompensation	3	13.0
Pneumonia	1	4.4
Uremia	1	4.4
Total	23	

The relation of the deaths to the indications for cesarean section is presented in Table 9. There were 5 deaths among the patients with repeat cesarean section. Two of these were from spinal anesthesia, and 1 from aspiration of vomitus during inhalation anesthesia, all of which occurred before the present well trained anesthesia service assumed the responsibility of this important phase of obstetrics. One patient died of secondary hemorrhage twelve hours after operation. The fifth death was from embolus (proved at autopsy) one hour after delivery (the only unavoidable death in the group).

Five deaths occurred among the patients with disproportion. Three died from sepsis, and 2 of these cases had been mismanaged outside the hospital. All these cases occurred before the days of the sulfonamides and penicillin. One patient, who died from hemorrhage on the twenty-third post-partum day, had had several episodes of moderate bleeding before the fatal hemorrhage and should have had a hysterectomy early in the post-partum period. There was 1 death from embolism in this group.

In the cases of placenta previa there were 4 deaths. One was from sepsis, 2 from hemorrhage, and 1 from lobar pneumonia before the days of the antibiotics.

There were six deaths from separated placenta. Four patients died from shock and hemorrhage, 1 from uremia and cortical necrosis on the third post-operative day, and 1 from embolism on the fourteenth day.

Table 9. *Deaths in Relation to Indications for Cesarean Section.*

Indication	Total No. of Cases	No. of Deaths	Mortality %
Repeat cesarean section	606	5	0.8
Disproportion	141	5	3.5
Placenta previa	68	4	5.8
Separated placenta	57	6	10.5
Cardiac decompensation	4	3	75.0

Of the 4 patients with cardiac disease who underwent cesarean section while decompensated, 3 died. Two died of typical cases of cardiac decompensation (both elderly primiparas, aged forty-two and forty respectively), 1 in eight days and the other in six days. The third patient died in eleven days from an embolism.

Conclusions

On the basis of these statistics certain axiomatic facts pertaining to cesarean section may be deduced.

Hemorrhage and sepsis are the most common causes of mortality from cesarean section.

Whole blood given early, rapidly and copiously is the only way to combat hemorrhage. Too often, transfusions are given too late, too slowly and in too small amounts.

Cesarean section must not be done in the presence of shock. Shock must first be treated as expeditiously as possible.

One must be sure there is no chance for secondary hemorrhage either from uterine atony or from improper hemostasis before the abdomen is closed.

Cesarean section has a distinct place in the treatment of toxemia and does not add to the risk especially if done under local or sodium pentothal anesthesia.

There is no limit to the number of cesarean sections that a patient may undergo, provided sufficient attention is given to the uterine scar both before and at operation.

The danger in cesarean sections after rupture of the membranes and prolonged labor is sepsis. Therefore, every patient in whom cesarean section is probable, when given a test of labor should receive sulfonamides and penicillin prophylactically after the first twelve hours. In the frankly infected cases the extraperitoneal operation should be done.

Cesarean section in cardiac cases offers no advantage over delivery through the pelvis and should not be done unless there is some other indication.

Anesthesia for cesarean section must be administered by a trained anesthetist, especially if one decides to use spinal anesthesia.

With proper attention to these suggestions the mortality for cesarean section should be kept below 1 per cent.

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HOSPITAL ADMINISTRATION AS A CAREER

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THE doctor's prescription has been one of the most important characteristics of the medical profession throughout the ages. It is as much the symbol of the medical profession as the mortar and pestle of the profession of pharmacy. Men doubtless prescribed in the dark before they elaborated the wherewithal to diagnose. The earlier the prescription, the greater appears to have been the element of chance with which our professional ancestors approached their patients. It is still the rod and the staff that comfort the patient, if not the practitioner. Even the placebo carries a world of meaning. Nothing justifies a fee like a prescription, and that is why the practitioner in search of the Holy Grail avoids medicine that is odorless, colorless and tasteless. One need only ponder over the slowness with which the pharmacology laboratory is arriving in the hospitals of today to understand the tenacity of sentiment versus science in prescription writing. The pharmacy is still patronized more for the products of the nostrum vendor and the quack than for the tested remedies of the man of science. The incantations of primitive man have their unhappy survival in the hit-or-miss prescriptions that belie our scientific pretensions.

Those who are still in the academic stages, and those who are serving clinical apprenticeships, know much better about the needs of the patient than their ancestors did. Modern practitioners of medicine are not so helpless and need not tolerate the shotgun methods of yesterday. If they do, it must be for a compelling reason, and I suggest that the dilemma be thoughtfully weighed.

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Though the principles and practice of social medicine are not yet taught in medical colleges and hospitals with the pedagogic energy that is expended on prescription writing, one cannot help becoming aware of its arrival, its staying power and its influence on this dilemma. Our descendants will be more keenly aware of its possibilities for good than we can be at present. Since we are confronted with this humanized concept of medical practice, we cannot help taking notice of it and should want to know more about it. For those who have aptitude for the practice of social medicine and are so constituted that they can find joy in it, new and bright horizons will appear. The doctor, in the role of social agent, has limitless possibilities. If, working in such an enlightened kind of medical practice, he finds a substitute to replace the fee-for-prescription method of compensation that dominates the individual practice of medicine (which, incidentally, must struggle with such a handicap to be scientific) he opens the doors of a room that is dimly lit and lets the sunshine in so that others, too, can benefit.

In recent decades of world upheaval, we have been taught many severe lessons that have brought home to us the broad concept of social medicine, in which the prescription is only one of many symbols. The practitioner is already beginning to merge his personality into this new concept, and he is doing it as an instrument of a sympathetic society. Before this development can proceed, however, someone must assume leadership and help to plan, build, organize and administer, to the end that we shall have worthy officership in this new army of practitioners. These officers should be located at general

headquarters, as well as in field headquarters, and the hospital qualifies admirably for either purpose.

According to the new trends, the hospital is beginning to emerge as the hub of medical activity. Radiating from its central diagnostic and therapeutic facilities, and serving the community as an integral part of it, are the outpatient department, the doctors' office building (which will bring the doctor closer to his workshop), the department for continued care (which will discharge a debt that has been owing for some time to the long-term patient), the department of psychiatry, the department of tuberculosis (if this illness is not brought under control sooner — and even if it is), the group-practice unit (for an insured group of patients), the health center, the convalescent unit and the preventorium. Hospital care in the home will also radiate from such a center and serve patients extramurally on an extension basis so that they will be cared for at all times and in all places, comprehensively. The practitioner never had a better friend than this kind of center promises to be, nor did the sick. He must, therefore, familiarize himself with its possibilities for good in his professional life as a man of science, unless he wants to remain a prescription writer who continues to practice uncritically, forever, what he was taught to prescribe in medical school. Each one of the activities revolving around the hospital calls for executive talents of a high order, and each one is beckoning to the young house-staff graduate who has the imagination, the vision and the other qualities of leadership to take advantage of such opportunities.

Hospital administration as a career is not limited to medical men, but medical men possess advantages, whereas laymen must overcome handicaps in this kind of executive work, which calls for considerable medical knowledge as well as social insight. It has been said that the hospital executive must also be a good "businessman" and that the layman has the edge on the physician in this respect, but this requirement is more apparent than real and is not based on actual experience in the hospitals of this country. This is not to deny that good business judgment is helpful to the medical executive. In the long run, however, medical knowledge, medical objectives and medical opinion must be sought and considered.

There was never a time in medical history when the need for qualified medical executives in hospitals and elsewhere was greater than it is today. The opportunities for qualified men are endless, with new areas for creative work opening up daily, and the conditions of service are favorable. The medical executive is able to live a full and useful life, with credit to himself and his family. Riches are not to be sought in the professions in any case. Medical executives live in comfortable material circumstances, unworried by profit motives, and are assured a continuous income, which is seldom inadequate. The reduction of the overhead costs, which must be balanced against income, is only one comparative aspect of the matter.

It is said, of course, that the medical executive must surrender some of his independence when he becomes subservient to a board of trustees, — of whom, by the way, he is always a few jumps ahead in the program if he is worth his salt, — but independence to do what? To be legally free, as some are, to practice alone while the four walls, like dead men, tell no tales? To charge whatever the traffic will bear, as some do, while rebelling inwardly at the necessity for such compromises with the high code of medical ethics taught in medical schools? The practitioner will become the man of science that he deserves to be, and ought to be, when he or his colleagues will stand up and, through the kind of leadership here outlined, challenge the prevailing method of distributing medical care.

No doubt the practitioner, be he physician, surgeon or specialist, is attracted by the more dramatic forms of medical practice. As a medical executive, I envy the surgeon his joy when a patient on whom he has performed a successful laparotomy is discharged cured, after a short stay in the hospital, though an occasional patient may be lost. His results are more tangible in terms of space and time. But the cures of the medical executive reach out into a wide area of space and cover a long period. Though the results of his planning are not so immediately visible, or heartwarming, to the medical executive they reach far more people and their effects often make medical history. Without the planner, the practitioner toils laboriously in vain.

Medical executive work, by its very nature, brings the rewards of good companionship. Work on the frontier is always exhilarating to the pioneer, and he is forever rubbing elbows with others whose outlook on medical life is similar to his own. The related specialties are close. Social service becomes a prize prescription, with a wealth of vital ingredients — none of which, by the way, act mysteriously. Social medicine, which is the practice of medicine in relation to all the social forces that influence our lives, is a more intelligible and more life-giving concept than the limited form of medical practice that preceded and survived the advent of the social sciences. It should therefore be cultivated for its worth and should attract qualified leadership.

The opportunities for full-time executive medical service are many, and these are knocking at the doors of young physicians who are prepared to put in an additional apprenticeship in administrative medicine. Schools for hospital administration, with mixed lay and medical student bodies, have come into vogue in recent years and provide an academic year of university training on a graduate level, followed by an administrative internship of a year leading to a master's degree. The alternative to this

kind of formal preparation is an apprenticeship to a good teacher, under whom the student qualifies in the school of experience. A combination of both is undoubtedly the best kind of preparation. In any case, the student should allow five years for seasoning from the time of his graduation from the house staff of a hospital before seeking an independent executive position where much will depend on his maturity of judgment. Apprenticeship of this kind, unlike the advanced residencies in clinical medicine, pays a good living wage, and the rest can safely be charged up to investment by an ambitious and self-confident student. Dividends start flowing early because the opportunities are so great.

For the future medical executive there opens up a world of opportunity and one that remains unmatched in the learned professions. For those whose aptitudes and preferences are in clinical medicine, there are additional worlds to conquer, but these worlds will be conquered faster and more completely through a proper distribution of personnel where each can do the most good in his own way.

MEDICAL PROGRESS

CHEMOTHERAPY OF NEOPLASTIC DISEASE

II. Trends in Experimental Cancer Therapy

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The cancer chemotherapist, in the absence of a fundamental philosophy or a satisfactory approach to his problem, is an eclectic, borrowing ideas and discoveries from the more advanced or at least the more fruitful scientific disciplines. The range of his interests and the nature of his approach are shown in the number of chemicals and groups of substances under study. These agents are, for the most part, chiefly of interest in a historical and immediate sense for many, if not all, will ultimately be discarded. Until a fundamental discovery appears, each year will see new agents greeted with enthusiasm, and each decade will see some of these compounds through a cycle of interest and sometimes enthusiasm — created in various ways — and then active rejection or passive disuse. These cycles, of course, leave a residuum of basic and useful information that will make subsequent work more efficient and critical and from which, some day, important contributions may develop. In the following paragraphs the major current trends in cancer chemotherapy are reviewed, with emphasis on substances under recent clinical trial.

BIOLOGIC PRODUCTS

Bacteria, Molds and Protozoa

Coley's mixed toxins. In 1892, acting on the reported clinical observations that attacks of erysipelas in patients with inoperable cancer were sometimes associated with permanent or temporary tumor regressions, Coley began to use killed cultures of virulent streptococci isolated from patients with erysipelas in the treatment of cancer. Subsequently, *Bacillus prodigiosus* (*Serratia marcescens*) was added to the cultures, since this organism was believed to increase the virulence of the streptococci. Vaccines of this general type were used for a number of years in many parts of the world. In spite of the occasional favorable reports, the therapeutic activity of the vaccine appears to have been inconstant and unpredictable, and its use was gradually abandoned. Apparently, an important factor in preventing an acceptable or definitive evaluation of Coley's toxins lay in the variability of the preparations used and the different dosages and technics of administration. In an effort to revive interest in this form of treatment, recent historical reviews of Coley's toxins have appeared.[37,38] These reviews do not enhance the status of the agent, or present any compelling reason for its further clinical use. As an approach to cancer chemotherapy, Coley's work has anticipated and encouraged the modern investigations on purified bacterial toxins.

Shear's polysaccharide. In 1931 Gratia and Linz[39] reported that bacterial filtrates produced hemorrhages in a transplanted tumor in the guinea pig. Zahl and his group[40–42] tested a large number of bacterial filtrates and suspensions against Sarcoma 180 in mice, and found that the hemorrhage-producing substances occurred chiefly in gram-negative organisms, and were probably endotoxin antigens. Under the direction of Shear[18] an extensive co-operative study has been in progress on the isolation, characterization and mechanism of action of the hemorrhage-producing substance found in *B. prodigiosus* filtrates. The active material is homogeneous by electrophoresis and ultracentrifugation.[43,44] Chemically, it appears to be composed chiefly of polysaccharides with small amounts of phospholipid and nitrogen in several unidentified

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forms.[45] The material is not inactivated by trypsin. It is extremely toxic to mice; a dose of 0.01 mg. (about 0.5 mg. per kilogram of body weight) in mice weighing 20 gm. will produce a significant mortality. It is antigenic and after repeated injections, larger doses are needed to produce a toxic effect. In mice a toxic dose of the polysaccharide will cause a fall in body temperature[46]; in rabbits and mice it is a pyrogenic agent.[47]

The purified agent on parenteral administration, at doses not injurious to the normal tissues, will induce hemorrhage within a few hours, followed by necrosis and partial regression of transplanted and spontaneous mouse tumors.[48] Mitotic activity in the tumor disappears one and a half hours after the injection of a maximum tolerated dose; the nuclei swell and then become pyknotic.[49] There is a fall in the blood flow in the tumor capillaries, numerous petechiae appear, and the blood flow finally ceases.[50] Several days later new capillaries begin to form at the periphery of the tumor with multiplication of the surviving tumor cells. The polysaccharide does not show any selective toxicity to cells in tissue culture.[51] The general interpretation of effect is that the polysaccharide acts by producing a "shock-like" state; the blood supply to the vulnerable capillaries in the tumor is decreased, and edema, hemorrhage and necrosis may then develop in the tumor. There is no satisfactory evidence of a direct toxic effect on the tumor cells.[50]

The purified polysaccharide was first used clinically by Brues and Shear[52] on several different types of tumor in 4 seriously ill patients. The agent, in very small doses, produced a high fever, leukocytosis and a fall of blood pressure, frequently to shock levels. Hemorrhage into the tumor and occasionally a decrease in tumor size were observed. Holloman[53] and Oakey[54] have reported their experiences on a total of 17 cases with a variety of tumors. The treatment appears to be hazardous, but the tumors sometimes regress and occasional temporary clinical improvement develops. Shear's group states, however, that the purified polysaccharide is not considered suitable for general clinical use.[18]

Crude penicillin. Cornman[55] observed that crude penicillin was injurious in tissue cultures to several types of rat and mouse sarcomas at concentrations that did not damage normal fibroblasts. This selective effect was not found with purified penicillin.[56, 57] The penicillin impurity exerting this selective effect in tissue culture has not been identified.

Studies of the effects of a variety of mold filtrates and extracts on the neoplastic cell are now in progress.[58, 59] Cohen, Borsook and Dubnoff[34] tested a variety of micro-organisms by an in vitro technic for disclosing carcinoclastic microbial products, and they report that cultures of *Sporosarcina ureae* contain a substance injurious to tumor cells. Kidd[60] has reported that culture filtrates of *Aspergillus fumigatus*, presumably containing gliotoxin, were injurious to tumor cells in vitro, but this extract has not proved effective thus far against tumors in vivo.

K-R. An endotoxin prepared from killed *Trypanosoma cruzi* (the causative agent of Chagas's disease), developed by Roskin[61] and Klyueva[62] and appropriately named K-R, has been reported to be effective in treating cancer in mice and man. In tumor-bearing mice infected with *T. cruzi*, Roskin observed a concentration of the organisms in the tumor, associated with destructive and regressive changes. Infections with *Borrelia duttonii* (*Spirochaeta duttoni*)(relapsing fever) and *Trypanosoma equiperdum* (dourine) were without effect on the tumors. Roskin, with the assistance of Klyueva, then prepared an endotoxin from *T. cruzi* that was also found to damage neoplastic cells. Regressions in Sarcoma 180 and Ehrlich's carcinoma of mice and in the Flexner–Jobling carcinoma of rats were produced without injury to normal tissue. If tumor cells were soaked in a K-R solution prior to implantation in mice, they failed to "take." The active material was water soluble, retained its activity after heating at 50°C. for twenty minutes, but it lost its potency within ten to twelve days when kept at 1°C. in the liquid state.

In 1941 K-R was first used in the treatment of patients with cancer. The subcutaneous, intramuscular or intratumoral injection of K-R caused cancers to disintegrate. Five out of 10 carcinomas of the larynx, 3 carcinomas of the cervix and 3 out of 5 carcinomas of the breast regressed remarkably under treatment. The beneficial effects varied directly with the dosage; large doses, however, caused a high temperature, and treatment was temporarily stopped. One unit was standardized as 1,000,000 *T. cruzi* organisms, and a course totaling 755 units has been given to a single patient.

The Russian reports of the remarkable results achieved with K-R therapy prompted confirmatory studies in this country. Hauschka[63–65] has carried out the most extensive work, using eight different strains of *T. cruzi*, including the one used by Roskin, against five types of tumor in mice. Mice infected with *T. cruzi* showed consistent retardation of tumor growth and occasional tumor regressions, but this was related to the virulence of the strain and the lives of the mice were not prolonged. The parasites did not concentrate in the tumors, as stated by Roskin; in fact, the cancer cells proper were only rarely parasitized, whereas the visceral organs and skeletal muscles were heavily infected. One virulent strain produced suppression of tumor growth coincident with weight loss and death eight to thirteen days after inoculation, but if the infection was checked with the quinoline derivative, Bayer 7602, tumor growth was resumed. Killed cultures and lysates of *T. cruzi* were without effect on tumor growth in mice,[64, 65] and Cohen, Borsook and Dubnoff[34] were unable to demonstrate any effect of *T. cruzi* on mammary carcinoma and Brown–Pearce

carcinoma by tests in vitro. Malisoff,[66] however, reported that by means of K-R preparation he produced complete regression of 55 per cent of tumors (Sarcoma 180 and a spontaneous mammary carcinoma) in mice, but his work has been severely criticized.[65] In view of the general failure to confirm the laboratory aspects of Roskin and Klyueva's work, clinical trials with K-R are not indicated.

Urine and Tissue Preparations

H. 11. H.11 is an extract of normal human urine reported to contain growth-inhibiting substances.[67] One group of workers has found that it slowly but ultimately inhibited the growth of the Twort carcinoma in mice,[67] but others were unable to demonstrate any therapeutic effect on mouse tumors.[68, 69] Since 1941, H.11 has been used in England for the treatment of inoperable carcinoma, but the remarkable therapeutic effects attributed to it have not been confirmed.[70]

Myelokentric acid. Miller, Wearn and Heinle,[71] in 1939, described substances obtained from the urine of leukemic patients that induced stimulation of the myeloid and lymphoid systems in laboratory animals. Subsequent study by Heinle et al.[72] led to the conclusion that a substance can be extracted from the urine of patients with chronic myelogenous leukemia that will induce myeloid metaplasia in guinea pigs. The substance responsible for this effect appeared to be protein in nature.

On the other hand, a more complicated situation is suggested by Turner and Miller.[73] In the urine of patients with chronic myelogenous leukemia, a substance that produced myeloid metaplasia was obtained, whereas, in chronic lympathic leukemia, the urine extract induced lymphoid metaplasia. These substances were named myelokentric and lymphokentric acid, respectively. In Hodgkin's disease and monocytic leukemia an intermediate effect in guinea pigs was obtained, and in these diseases the urine was found to contain a mixture of myelokentric and lymphokentric acids. Liver extracts contained both fractions. Extracts of myeloid leukemic tissue produced myeloid metaplasia, and lymphoid leukemic tissue, lymphoid metaplasia; tissue extracts from patients with Hodgkin's disease tissue caused a mixed reaction in the guinea pig.[74]

Miller, Herbut and Jones[75] have treated 8 patients with lymphoblastic leukemia with crude myelokentric acid. They observed 13 partial remissions in these patients, and at autopsy the disease appeared altered by the treatment. They do not recommend this treatment because the preparation is crude, it is very difficult to obtain, and there is no standard dosage.

Splenic extracts. For many years, splenic extracts and preparations containing spleen, such as "splendothelan" and "aristotrop,"[1] have been proposed for the treatment of cancer, and all have fallen into disrepute. Recently, however, it was reported that a splenic extract induced tumor regressions in mice and definite improvement and tumor regression in 3 patients with carcinoma.[76]

A.C.S. Human spleen has been used as an antigen in rabbits to produce an antiserum, the "antireticular cytotoxic serum" or A.C.S. This substance has been proposed by Bogomolets[77] as a formidable adjunct in the treatment of many diseases, including cancer. In inoperable cancer, he has reported that its use may reduce pain, improve the general condition of the patient, cause metastases to regress and sometimes prolong life. A.C.S. made from mouse spleen will inhibit tumor transplants in mice, and rat A.C.S. will inhibit the growth of the Walker rat Sarcoma 319 in vitro.[78]

Two clinical reports on A.C.S. have appeared in this country.[79, 80] In a preliminary report on 106 cases, Davis[79] observed occasional relief of pain, gain in weight, increase in appetite and a sense of well-being. One patient with myeloid leukemia showed a fall in white-cell count with each course of treatment. A.C.S., however, could not be shown to prolong life. The usual course of treatment was 0.5 cc. of the serum on the first, 1 cc. on the fourth and 1.5 cc. on the seventh day; courses were generally repeated every six weeks. Skapier[80] used the same dosage schedule in patients with Hodgkin's disease, and he observed a decrease in the sedimentation rate in 10 and a gain in weight in 12 out of 22 patients. There was no significant regression in enlarged lymph nodes. A.C.S. does not appear to have any specific action in neoplastic disease, but Bogomolets's approach is of considerable interest.

Boyland[81] fed tumor-bearing mice various muscle extracts. The most effective inhibition of tumor growth was produced by extracts containing ethanolamine or cadaverine hydrochloride. Mouse carcinoma 2146 mixed with histone or protamine prior to inoculation showed a definite but transient decrease in growth rate, whereas human plasma or egg albumen did not have this effect.[82] The pentose nucleotides were injected into mice implanted with methylcholanthrene sarcomas; adenylic and guanylic acids inhibited tumor growth but also caused amyloidosis; cytidylic acid had little effect, and uridylic acid stimulated tumor growth.[83] Several dipeptides and d,l-dipeptides and polypeptides were found to have no effect on the growth of mouse and rat tumors.[84]

Vitamins

The accessory food substances have been examined for their role in cancer growth, either by giving an excess of the vitamin or by producing a specific vitamin deficiency. A deficiency may be produced by dietary restrictions or the administration of specific antimetabolites.

Biotin. As a result of the demonstration that biotin was essential for animal growth and that avi-

din, a protein contained in egg white, antagonized biotin, Laurence[85] suggested that avidin might be useful in the treatment of cancer. Mice on a biotin-deficient diet and mice fed large amounts of avidin showed no decrease in the rate of tumor growth.[86, 87] The feeding of large amounts of egg white to a total of 12 patients with cancer produced no clinical evidence of a biotin deficiency and no alteration in the course of the disease.[85, 89]

Paraminobenzoic acid (PABA). The influence of paraminobenzoic acid on chronic leukemia was examined by Zarafonetis et al.[90] It was given orally to 10 patients with chronic leukemia in doses of 2 to 4 gm. every two hours, so that a blood level of 10 to 30 mg. per 100 cc., and frequently higher, was maintained. This dose produced a fall in white-cell count, usually after two or three weeks of treatment. When treatment was discontinued the white-cell count promptly rose. While the drug was being given, some of the patients showed a partial clinical remission, which was slight and transient. The effects were more striking in chronic myelogenous than in chronic lymphatic leukemia. There is no suggestion that PABA has a significant therapeutic effect in leukemia. Bichel,[91] on the other hand, has reported that PABA will raise the white-cell count in leukemia.

Pyridoxine. The growth of the Flexner–Jobling carcinoma in rats and 2 different transplantable tumors in mice was decreased on a pyridoxine-deficient diet.[92] A potent pyridoxine antagonist, desoxypyridoxine, when given to mice on a pyridoxine deficient diet, inhibited the growth of a transplanted lymphosarcoma.[93]

Teropterin. Lewisohn and his group[94–96] reported that spleen extract, extracts of the spleens from mice cured of Sarcoma 180 ("healed-spleen extract"), yeast extract, pearled barley extract, inositol and *Lactobacillus casei* factor (pteroyl-triglutamic acid, or teropterin), cured an appreciable percentage of mice inoculated with Sarcoma 180. The "healed-spleen extract" and pteroyltriglutamic acid also induced regressions in spontaneous mammary tumors in mice. Pteroylglutamic acid did not cause tumor regression.[97] Several other laboratories were unable to confirm these results,[98, 99] and there is no substantial laboratory evidence that pteroyltriglutamic acid has any influence on tumor growth.

In the past five years spectacular advances have been made in the chemistry and pharmacology of the folic acid compounds, pteroylglutamic acid and its conjugates.[100] Pteroylglutamic acid and pteroyltriglutamic acid (teropterin) produce hematologic remissions in pernicious anemia, nutritional macrocytic anemia and sprue.[101] In laboratory animals no significant qualitative differences in the pharmacologic actions of the pteroylmonoglutamic and triglutamic acid forms have been described.

On the basis of Lewisohn's work, Farber et al.[102] studied the effects of pteroyldiglutamic and triglutamic acid on a series of 90 patients with a variety of neoplastic diseases. They found that these agents given intravenously or intramuscularly had no immediate or delayed toxicity or unpleasant side-effects. On the basis of their clinical experience, they recommended a daily dose of 20 mg. Patients were reported to feel better, showed an increase in energy, appetite and sense of well-being, and a diminution in apprehension and pain. Furthermore, in some of the treated cases, the tumors showed histologic changes that could be attributed to therapy. Lehv et al.[103] claimed that teropterin reduced the narcotic requirements of patients with inoperable cancer. Teropterin is now being sold as a palliative agent in cancer. It is therefore important to note that the therapeutic effects ascribed to teropterin are couched in such tenuous and devious terms that they defy critical analysis. In the absence of reproduceable and consistent objective evidence of effect on neoplastic disease, teropterin cannot be regarded seriously as a chemotherapeutic agent against cancer.

Several folic acid antagonists have been prepared.[104] Meyer,[105] in a preliminary report, studied the effect of two of these compounds on acute leukemia. He observed a transient remission in 3 out of 5 cases. More recently, an extremely toxic folic acid derivative, 4 amino-pteroylglutamic acid (aminopterin), has been under study. This material does not behave in animals like a typical folic acid antagonist, and it appears to have toxic properties of its own. It has recently been reported to induce temporary remissions in acute leukemia in children.[106]

Hormones

Studies of the therapeutic effects of the sex hormones on tumors arising in sex-linked organs have been conducted almost entirely in man. It is extremely difficult to obtain transplantable animal tumors that are sensitive to the influence of sex hormones; androgens[107] and estrogens[108] have little influence on the growth of the commonly used mouse tumors. In man, the therapeutic effect of the several types of estrogenic hormones on carcinoma of the prostate is attributed to estrogenic activity per se. It is of interest that alpha-bromo-alpha, beta, beta-triphenylethylene, a relatively weak estrogen as compared with stilbestrol, is stated to be unusually effective in the treatment of prostatic carcinoma.[109]

The adrenocortical hormones, which are involved in the metabolism of lymphatic tissue, have been shown to affect tumors of hematopoietic origin in mice. Heilman and Kendall[110] reported that 11-dehydro-17-hydroxycorticosterone (compound E), when given orally or parenterally, will produce a temporary regression of a transplantable lymphosarcoma in mice. This effect was more consistent in female mice or castrated male mice. Murphy and

Sturm[111] have found that treatment with the adrenocortical hormones or the pituitary adrenotropic hormone decreased the susceptibility of rats to a transplantable lymphatic leukemia. Law and Speirs[112] have described profound palliative effects, marked tumor regression and possibly some prolongation of life in mice with spontaneous lymphoid leukemia treated with adrenocortical extracts.

Cell Poisons

There are a number of cellular poisons that, in the normal animal, are injurious to the more actively growing tissues (chiefly those of the blood-forming organs and the gastrointestinal tract). None of these agents have been shown to have a highly selective effect on cancer cells, per se, but certain tumors are temporarily more sensitive to these agents than the most susceptible of the normal tissues. Many of these agents, therefore, have been tested, and some are used extensively in the palliative treatment of cancer.

Nitrogen Mustards

The nitrogen mustards have the fundamental structure $\begin{matrix}ClC_2H_4\\ClC_2H_4\end{matrix}>N\text{-}R$. The *bis* (beta-chloroethyl) group is essential for the toxic characteristics of these agents (although certain minor modifications do not change its activity qualitatively), whereas the R group may be varied considerably without alteration of the essential characteristic pharmacologic actions of the molecule. Under physiologic conditions, active members of this group undergo rapid intermolecular rearrangement with the loss of a Cl to form an imine linkage. This is illustrated by the most common nitrogen mustard studied, methyl *bis* (beta-chloroethyl) amine hydrochloride $Cl^-\begin{matrix}ClCH_2CH_2\\CH_2CH_2\end{matrix}>\overset{+}{N}\text{-}CH_3$. The imine linkage is the reactive part of the molecule, reacting with a great number of biologic substances. The pharmacologic action of the nitrogen mustards has been reviewed,[113–115] and their toxic actions from a physiologic[116, 117] and a pathologic point of view have been described.[118, 119] These compounds have been shown to produce cytologic damage,[120–122] mutations in Drosophila[123] and Neurospora[124] and selective effects on differentiating embryonic cells.[125] Their radiomimetic effects have been emphasized.[114, 119] Alterations in their chemical structure have produced marked changes in their pharmacologic activity.[114, 115, 126, 127]

The nitrogen mustards (and the closely allied sulfur mustards) exert an inhibitory effect on the growth of certain mouse tumors,[128, 129] prolong the life of mice with transmitted leukemia,[26] selectively inhibit the growth of the mouse Sarcoma 180 on the chorioallantoic membrane of the chick embryo[28] and exert a therapeutic effect on fowl leukosis.[31]

Burchenal and his associates[26] have examined the activity of a large number of nitrogen mustard analogues in prolonging the life of mice with transmitted mouse leukemia. They found that, in general, the quaternary ammonium compounds and the mono- (beta-chloroethyl) group compounds were inactive, whereas the bis (beta-chloroethyl) groups and bis (beta-bromoethyl) groups and diamine mustards with 4 beta-chloroethyl groups were active in prolonging life. There seemed to be a direct correlation of the radiomimetic toxic effect of a nitrogen mustard and therapeutic activity.

The clinical use of methyl-bis (beta-chloroethyl) amine hydrochloride (HN2) is discussed in the next section. Two nitrogen mustard derivatives, 1:3 propane diamine (NNN′ N′ tetrakis [2-chloroethyl] [SK136]) and 1:3 chloropropyl diamine (NNN′ N′ tetrakis [2-chloroethyl] [SK137]), which showed therapeutic activity against mouse leukemia, have been tested clinically.[130] Although these agents do not seem to produce as much nausea and vomiting as HN2, they cause dizziness and, occasionally, toxic psychoses, and therapeutically, they do not appear to be more effective than HN2.

Urethane

Ethyl carbamate is a relatively simple organic chemical with the following formula: $H_2N\begin{matrix}COC_2H_5\\C=O\end{matrix}$. It had been known for many years to exert a suppressive effect on growth processes, but interest in this agent in relation to neoplastic disease is only of recent origin. In 1939 Lefevre[131] described abnormal development and retarded growth in seedlings exposed to ethylphenyl carbamate. Templeman and Sexton[132] undertook a systematic survey of the aryl carbamates and related substances as plant-growth inhibitors. They found isopropyl phenylcarbamate to be most effective; urethane and methyl carbamate were inactive. Haddow and Sexton,[133] therefore, examined the effects of carbamates on tumor growth in animals. Phenyl urethane and urethane proved to be equally effective in inhibiting the growth of spontaneous mammary tumors in mice and the transplanted Walker carcinoma 256 in rats and, among the members of the carbamate series tested, these substances were unique in having this effect. Subsequently, numerous confirmatory reports appeared, demonstrating the suppressive action of urethane on rat Sarcoma 39,[134] transplanted lymphatic leukemia in rats[135] and transplanted[26, 136–139] and spontaneous[140] leukemia in mice. The clinical application of urethane is discussed below.

In addition to the suppressing effect of the drug on tumor growth, the demonstration that urethane was carcinogenic also aroused interest. In 1943 Nettleship and Henshaw[141] reported that urethane administration induced pulmonary adenomas in mice, and a similar action has been recorded in

rats.[142] An extensive literature now exists on the carcinogenicity of urethane. Larsen[143] has shown the remarkable specificity of the carcinogenic activity of ethyl carbamate; methyl carbamate is ineffective, and isopropyl carbamate has one-twentieth and n-propyl urethane one-eightieth the carcinogenic activity of urethane.

Dustin[144] found that the parenteral administration of urethane to mice reduced mitotic activity and produced cellular degeneration in the intestinal mucosa. There was a decrease in the reticulocyte count in the peripheral blood of rabbits and a slight shrinkage in the size of lymph nodes, but injury to the bone marrow was not apparent.[145] Some hematopoietic injury can be produced in man with urethane,[146] and this may be due to the greater sensitivity of the human bone marrow as compared with that of lower animals. Urethane appears, therefore, to act as a mild cell poison in vivo. Vascular and parenchymal liver injury[147] and liver tumors[142] have been reported in rats treated with urethane.

Colchicine

Colchicine, an alkaloid obtained from the autumn crocus, is a mitotic poison, arresting cell division in the metaphase. It has been shown to induce temporary regressions of lymphoid tumors[148] and to prolong life in leukemic mice.[26] Ludford,[149] in a review of colchicine in the experimental chemotherapy of cancer, concludes that "regression of tumor growth subsequent to colchicine treatment is primarily the result of hemorrhages following the disruption of newly formed capillaries." The effect of colchicine on animal tumors is not significantly enhanced when the drug is given in combination with x-ray therapy,[150, 151] bacterial toxins[152] or 2-methyl-naphthoquinone,[153] a substance with high vitamin K activity. A large number of colchicine derivatives have been tested against tumors, but none have shown any greater selective action than colchicine on neoplastic cells.[149]

Colchicine will induce an increase in mitotic figures in human tumors within twelve hours.[154, 155] Of 4 patients with advanced carcinoma treated with colchicine, 2 died within a few days, apparently of colchicine poisoning, with fever, diarrhea, pancytopenia and bleeding tendencies. The remaining 2 survived to show some tumor regression.[156] The dosage varied from 12 to 22 mg. in four or five days. It was concluded that although cancer cells are susceptible to colchicine, the concomitant toxic effect makes its use very hazardous. Colchicine was not found to be very effective in human leukemia,[157, 158] but the clinical trials were inadequate.

Podophyllin

Podophyllin, an extract of the dried rhizomes and roots of the mandrake plant, has been used for many years as a cathartic. It is composed of resins and an active principle, podophyllotoxin. When applied locally, podophyllin is effective in the treatment of condyloma acuminata, and a similar therapeutic effect has been obtained with colchicine.[159] Podophyllin also blocked mitosis in the root tips of *Allium cepa*.[160] Podophyllin and podophyllotoxin have produced hemorrhage in mouse tumors.[161] In tissue cultures, podophyllin and, to a lesser extent, podophyllotoxin have a selective damaging effect on mouse tumor cells.[32] Podophyllin appears to be similar to colchicine in many of its toxic effects.

Carcinogenic Agents

In 1935 Haddow[162] demonstrated that potent carcinogens, including 1:2:5:6-dibenzanthracene and 1:2 benzpyrene, inhibited the growth of the Jensen rat sarcoma; 9:10 dimethyl 1:2 benzanthracene inhibited the growth of Sarcoma 180[163] and prolonged the life and, in some cases, cured mice with transmitted leukemia.[164–166] This agent produced leukopenia, but leukemic mouse cells were more sensitive to its action than the normal white cells. Engelbreth-Holm and Stamer[167] treated 11 patients with 9:10 dimethyl 1:2 benzanthracene. The agent was suspended in a 2.5 per cent solution in distilled water, and was given intravenously in single doses, as large as 1 gm. daily, a total course consisting of 1 to 11 gm. The injection was well tolerated, but it produced fever, with some nausea. A brief clinical remission occurred in 1 of 5 patients with acute leukemia, a more prolonged remission developed in 2 patients with chronic myelogenous leukemia, and 2 patients with chronic lymphatic leukemia showed definite improvement. The treatment was without effect in 2 patients with multiple myeloma.

Seligman et al.[168] have synthesized a number of noncarcinogenic hydrocarbons related structurally to the carcinogens. These agents were tested for chemotherapeutic activity in transmitted myeloid leukemia, mammary adenocarcinoma and fibrosarcoma in mice. None of these compounds, or their carcinogenic analogues, prolonged the life of leukemic mice, but some compounds inhibited the growth of solid tumors.

The carcinogenic activity of another class of carcinogens, the aminostilbenes, was detected because it was first found to inhibit tumor growth.[169] Clinical trials have been started with 2′ methyl and 2′ chloro-4-dimethyl aminostilbene, but the difficulties of administration have, thus far, not been overcome.[170] Boyland[170] has commented on the fact that the carcinogenic agents are the ones that have proved to be most effective in the treatment of cancer; these include x-rays, Fowler's solution, urethane, estrogens and the nitrogen mustards (several mice treated chronically with this agent have developed tumors).[171]

Flory et al.[24, 25] tested a variety of substances against several strains of transmitted leukemia. *Potassium arsenite* and *benzene*[172] were effective in

prolonging the lives of leukemic mice, and one type of leukemia (L1394) was cured occasionally with benzene. Other organic arsenicals and benzene derivatives tested were less effective.

Radioactive Substances

X-rays or radioactive isotopes, which injure cells by their radiations, cannot be regarded as chemotherapeutic agents. Since one of the principles of isotope therapy, however, is the localization of the radioactive agents in certain tissues, the biochemical properties of the radioactive material are of great importance. The chemotherapist, therefore, has a fundamental role in this field. If he were to discover a substance that concentrated in certain types of tumors, it would be possible to make one or more of the atoms in this compound radioactive, and thereby specifically irradiate the neoplastic tissue. With this in mind, Bloch and Ray[173] have described methods for incorporating radioactive iodine in a variety of organic compounds.

Thus far, only radioactive elements have been tested as therapeutic agents in cancer. Radioactive phosphorus and iodine are in clinical use, and they are discussed below. Radioactive strontium concentrates selectively in areas of active bone formation, and it has been tried, with disappointing results, in the treatment of bone tumors.[8] Radioactive manganese (Mn^{52}), with a half-life of six and a half days, is given as a colloidal sol and it is taken up by the reticuloendothelial system. It has been used in the treatment of diseases of the hematopoietic system and allied disorders.[174] Colloidal radioactive gold (Au^{198}), with a half-life of two and three-quarter days, has been used more recently for this purpose.[175] Radioactive arsenic is an interesting isotope, but therapeutic trials with this agent have not yet been reported. Radioactive sodium (Na^{24}), with a half-life of fourteen and four-fifths hours, is evenly distributed throughout the body, and it provides a method for controlled total body irradiation. It has produced effects similar to total body irradiation in mouse leukemia.[176] Hahn and Sheppard[177] have analyzed the properties of radioactive isotopes that would make them suitable for therapeutic use. It is inevitable that a large number of radioactive isotopes and compounds containing radioactive atoms will be characterized and evaluated in the treatment of cancer.

Miscellaneous Compounds

Literally thousands of miscellaneous substances have been tested or are now under test for selective effects on neoplastic cells. They are greatly diversified, and they cannot easily be brought together.

Dyes

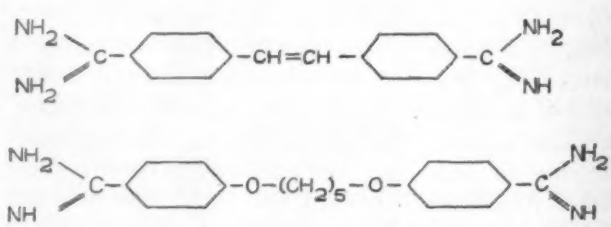
Many dyes have been tested in the hope of finding one that concentrated selectively in tumors. Zahl and Waters[178] tested a series of colloidal dyes, but could not demonstrate a selective uptake by tumor cells. The dye concentrated to some extent in the stroma surrounding the tumor, or at the interface of the viable and necrotic tissue. Boyland tested various derivatives of sulfonamides, and found that 4:4-diaminodiphenyl sulfoxide, sodium sulfanilyl-sulfanilate[21] and 4:4 diaminodiphenyl-ether[179] were most effective in temporarily inhibiting tumor growth in mice. The last compound, however, did not prove effective on clinical trial.[170] Lewis and Goland[180,181] tested a long list of acridine and other dyes by oral administration. Many of these stained tumors in mice and caused some retardation of growth; they did not prevent tumors from "taking" on transplantation or produce regressions in growing tumors.

Heptaldehyde

Strong[182] observed that heptyladehyde-sodium bisulfite, given in the proper dosage, caused regression and liquefaction in spontaneous mammary carcinoma in mice, although the regressions were rarely permanent. Boyland[20,183] tested a number of aldehydes, ketones and glucosides, and was able to report that, of these, citral and heptaldehyde inhibited the growth of spontaneous and transplanted tumors. Heptaldehyde sodium bisulfite methylsalicylate was selectively injurious in tissue culture to human and mouse mammary carcinomas and to rat lymphosarcoma.[184] Although heptaldehyde appeared to have an excellent record in the laboratory as an effective chemotherapeutic agent against neoplastic cells, it proved to be ineffective on clinical trial in 11 patients with metastatic mammary carcinoma[185] and in 3 patients with lymphoma.[186]

Stilbamidine

Stilbamidine (4,4′-diamidinostilbene) and a derivative, pentamidine (4,4′-[pentamethylenedioxy] dibenzamidine), are drugs that have proved effective in the treatment of kala-azar.[178–189] The formulas, respectively, are as follows:



Because patients with kala-azar develop an elevated serum globulin, Snapper[190,191] used stilbamidine in multiple myeloma, a neoplastic disease in which a high serum globulin level is often present, with palliative results.

The mechanism of the action of stilbamidine in multiple myeloma is not definitely established, but several pertinent observations have been made. Kopac[192, 193] has shown that stilbamidine reacts with nucleic acid to form a relatively inactive product; he suggests that stilbamidine acts by producing a dissociation of the protamine-ribonucleate complex, with the formation of protamine and a relatively insoluble stilbamidine-ribonucleate complex. Snapper et al.[194–196] have described basophilic inclusion bodies that appeared in the myeloma cells after treatment with stilbamidine. These granules were shown to contain ribose nucleic acid. The inclusion bodies may develop one or two weeks after treatment has begun, persisting for many months. They occur most frequently in patients with disturbed protein metabolism — that is, in almost all patients with hyperglobulinemia and in most patients with normal serum globulin with Bence–Jones proteinuria, but in none of the patients with a normal serum globulin level without Bence–Jones proteinuria.[196]

Stilbamidine is made up as a di-isethionate salt, which is more stable and water soluble than the hydrochloride salt. The solution must be prepared immediately before use, and may be given intravenously or intramuscularly. If the intravenous injection is too rapid, flushing and a fall in blood pressure may occur. Aged solutions of stilbamidine have produced liver and kidney damage, but in a careful study of the toxicity of fresh stilbamidine, Arai and Snapper[197] were unable to show any untoward effects in the liver, kidneys and peripheral blood.

The unpleasant side action of stilbamidine therapy is the development of a facial neuropathy due to toxic degeneration of the principal sensory nucleus of the trigeminal nerve, usually appearing two to five months after treatment. It is characterized clinically by numbness, formication and itching, and a dissociation anesthesia evidenced by a loss of sensation to light touch. Ten out of 18 patients in the series of Arai and Snapper[197] developed this syndrome. The symptoms slowly subside, but the dissociated anesthesia may persist. Continuation of stilbamidine therapy does not seem to aggravate the symptoms.

The recommended dosage is a first injection of 50 mg., a second of 100 mg. and 150 mg. per dose thereafter. The injections are usually given every other day, but daily doses may be used. In most cases a total of 4 to 6 gm. of stilbamidine has been given over a period of four or five months. Snapper[191] considers it essential that the patient be kept on a diet low in animal protein to obtain a therapeutic effect.

The effect of stilbamidine therapy in multiple myeloma is chiefly limited to the relief of severe bone pain. This relief is reported to be so striking that a bedridden patient may begin to walk again after four injections, and it is suggested that ambulation be started cautiously since excessive activity may precipitate spontaneous fractures.[191] The bone pain may be alleviated indefinitely by therapy, and improvement has lasted for a year and longer.

Gibson and Pogge[198] have analyzed the results of a pooled survey of 186 cases of multiple myeloma treated with stilbamidine. Twenty-four and seven-tenths per cent experienced complete relief of pain, the predominating symptom, and 38.7 per cent obtained partial relief of pain. The remainder of the patients were either unaffected or made worse. In 76 of 99 cases studied by serial x-ray examination, there was no increase in the size of the lesions, although regressions were rare. Toxic effects on the blood or kidneys were not reported, but facial neuropathy has, thus far, developed in 30 patients. Stilbamidine had no influence on the course of lymphatic and myeloid leukemia, lymphosarcoma, Hodgkin's disease and carcinoma.[190]

The clinical data indicate that stilbamidine may be of value in the treatment of the severe and often disabling bone pain of multiple myeloma, but there is no satisfactory evidence that it allays the systemic effects, inhibits the extension or prolongs the course of the disease.

Rubenstein,[199] on a rationale similar to Snapper's, recently reported that an antimony-containing compound, neostibosan, produced relief of bone pain and basophilic granulations in the myeloma cells in multiple myeloma. He states that, "in general, our observations on antimony are strikingly similar to those of Snapper, using stilbamidine, a drug containing no antimony."

Enzyme Poisons

Many enzyme poisons have been tested in an attempt to inhibit tumor growth. Since tumor cells are deficient in catalase, Boyland[170] tested a catalase inhibitor, a-nitroso-B-naphthol. This compound inhibited the growth of mouse tumors at tolerated doses. Brunschwig et al.[200] found that sulfhydryl inhibitors, iodoacetate and maleate caused a retardation in tumor growth. Woodhouse[201] obtained tumor inhibition with malonic acid but not with succinic acid. Sodium fluoride, iodoacetic acid, malonic acid and sodium azide have been used clinically in the treatment of leukemia, lymphosarcoma and several types of carcinoma.[202, 203] Alterations in the neoplastic cells and temporary clinical remissions in acute leukemia have been attributed to treatment with one or more of these chemicals.

Kline et al.[204, 205] have tested a number of pure chemicals and plant hormones in vitro and in vivo. The plant hormones had some inhibiting effects on the tumor cells in vitro, but were ineffective in inhibiting the growth of tumors in mice and rats. Belkin[206] found di-(hydroxymethyl) peroxide to be without effect in spontaneous transplanted and carcinogen-induced mouse tumors. Suramin (Ger-

manin), an anticoagulant, inhibited the growth of lymphosarcoma in mice, and caused lymphocytic fragmentation.[207] Chambers et al.[208] demonstrated that tetraethyl and tetra methyl-o-phenylenediamine selectively damage neoplastic lymphocytes in tissue culture. Thiouracil[209, 210] was of no value in the treatment of leukemia. The injection of one of a variety of amino acids subcutaneously,[211] glycogen intravenously[212] or ethyl alcohol intraperitoneally[23] induced regressions in transplanted tumors in mice or rats.

Geshickter and Reid[213] have made oil-soluble organometallic compounds containing copper, cobalt, manganese, zinc, nickel and iron. Some of these compounds occasionally induced partial and temporary remissions in chronic and acute leukemia, and nickel monobutyl phthalate is reported to produce occasional favorable effects in some cases of carcinoma.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

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CASE 34331

PRESENTATION OF CASE

A twenty-five-year-old man entered the hospital because of blurring of vision.

During the year before admission the patient was occasionally bothered by shortness of breath on exertion, and three months before admission he noted the onset of moderately severe frontal headaches. One month before admission blurring of vision appeared, which rapidly progressed until it was unsafe for the patient to walk on the street. One week later the headaches became more severe, and periorbital edema was noted in the mornings. There were no episodes of fainting and no epistaxis or symptoms of cerebrovascular accident, no chills, fever, orthopnea, edema of the ankles or increased abdominal girth and no known urinary disease or symptoms.

At the age of six the patient had had an attack of polyarthritis for which he was hospitalized and following which a diagnosis of rheumatic heart disease was made. He was kept out of competitive sports until the age of sixteen, but during the succeeding years he played baseball and filled a job requiring considerable physical effort with no difficulty. Five years before admission he was turned down by the Army because his blood pressure was "a little high."

Physical examination showed the patient to be pale and chronically ill. The eyes showed bilateral congenital zonular cataracts, which somewhat obscured the view of the fundi; nevertheless, numerous flame-shaped hemorrhages, many exudates and a Grade I papilledema were seen. The neck veins were dilated and pulsating. The lungs were clear except for some fluid at both bases. The heart was enlarged, the border of cardiac dullness extending to the left, the sounds were loud and snapping, and there was a widely transmitted Grade III apical systolic murmur. The liver edge was nontender and was felt one fingerbreadth below the costal margin. Shifting dullness and a questionable fluid wave were made out. There was minimal pitting edema of the ankles and sacrum. Chvostek and Trousseau signs were both present.

The temperature, pulse and respirations were within normal limits. The blood pressure was 210 systolic, 135 diastolic.

The hemoglobin was 8 gm., and the white-cell count 13,000. Urinalysis showed a specific gravity of 1.008 and a +++ test for albumin; the sediment contained 10 to 20 red cells, 5 to 10 white cells per high-power field and many granular casts. The nonprotein nitrogen was 90 mg. per 100 cc., the total protein 4.48 gm. per 100 cc., with an albumin-globulin ratio of 1.41, the serum calcium 5.8 mg. and the phosphorus 9.7 mg. per 100 cc., and the phosphatase 2.9 units. The sodium was 136.9, the chloride 98, the carbon dioxide 19, and the potassium 7.7 milliequiv. per liter.

The patient's output of urine was very poor. He was given a small amount of 5 per cent dextrose in water intravenously and shortly thereafter suffered an attack of acute pulmonary edema. This was treated with morphine, cedilanid and tourniquets. He improved somewhat but then gradually lapsed into coma, developed numerous petechiae and died on the third hospital day.

DIFFERENTIAL DIAGNOSIS

DR. BERNARD M. JACOBSON: To summarize this patient's clinical course, we have the onset of probable rheumatic fever, with rheumatic heart disease many years before admission. Five years before admission he first learned that he had hypertension. About one year before admission he began to suffer dyspnea on exertion; in other words, the first indication of some complication of hypertension. For three months the symptoms consisted mainly of hypertensive encephalopathy and retinitis. We are dealing, then, with a young man who carried a hypertension for at least five years but who began to suffer from probable congestive heart failure one year prior to death.

We are told in the physical examination that the neck veins were dilated and pulsating. Physical signs of that sort make us think of right-sided heart failure or pericardial effusion or constrictive pericarditis. We think especially of tricuspid stenosis. Apparently no x-ray films of his chest were taken during the hospital stay. Is that right?

DR. JOSEPH C. AUB: Yes.

DR. JACOBSON: We would be interested to see the configuration of the heart. We know that we can miss abnormal configurations by physical examination. The lungs were clear. I rather interpret the loud snapping first sound at the apex as probably due to hypertension and hypertensive heart disease. On the other hand, with the widely transmitted Grade III apical systolic murmur, one wonders if he had a diastolic blow. I am sure that we all can miss atypical diastolic blows, especially in a person who already has evidence of heart failure. We would also like to know whether the second aortic sound was louder than the pulmonic or vice versa.

We have evidence later of ascites. The Chvostek and Trousseau signs were undoubtedly due to hypocalcemia. The hemoglobin of 8 gm. is not accompanied by a description of the stained smear, but I presume the red cells were fairly normocytic and normochromic; in other words, this was an anemia of the simple, chronic type seen in renal disease. From the study of the urine we get no specific diagnostic information. The picture of renal malfunction gives evidence of both diffuse glomerular and tubular irritation. The patient undoubtedly had been in renal failure for some time because of the nonprotein nitrogen of 90 mg. per 100 cc. by the time he came to the hospital. The total protein was rather low, 4.5 gm. per 100 cc., and does not show the albumin-globulin reversal that we see in such conditions as subacute glomerulonephritis. There was no edema, and one wonders about the accuracy of the figure of 4.5 gm. per 100 cc. There was a rather marked hypocalcemia — 5.8 mg. per 100 cc.; on the other hand, in view of the remainder of the picture, I doubt that we have to worry about primary hypoparathyroidism. This is a picture of hypocalcemia, with secondary clinical evidence of tetany that we see every so often in terminal renal insufficiency, regardless of cause. The serum sodium and chloride were within normal limits. The potassium was high, undoubtedly due to renal retention. The carbon dioxide combining power compared with the normal of 25 milliequiv. per liter was not markedly reduced. Most people in uremia at this stage of the game should have a more marked acidosis. The terminal episode of pulmonary edema following the intravenous infusion of dextrose and water is a common phenomenon in people with either congestive heart failure or severe renal insufficiency or both.

The presence of petechiae terminally is a common finding in renal insufficiency and denotes some type of vascular purpura. There is no question that the patient died of a combination of congestive heart failure — as evidenced by the symptoms and the distribution of the edema — and renal insufficiency or uremia.

What was the cause of the congestive heart failure? We know that this patient had hypertension long enough to produce hypertensive heart disease. At autopsy there may or may not have been evidence of myocardial infarction or myocardial fibrosis due to coronary-artery disease. What evidence have we that he had any other type of heart disease, such as rheumatic heart disease? I think it is of importance that he was told at the age of sixteen that he had rheumatic heart disease. He undoubtedly was known to have a murmur at that time. I think we have to say that he did have rheumatic heart disease, in addition to the hypertension. I do not believe there is any particular association in this case between the two conditions. Did he have mitral regurgitation, or did he have mitral stenosis? A good deal of the murmur may have been due to congestive heart failure, part of it, at any rate, to old rheumatic heart disease, and part to hypertensive heart disease. I am a little surprised at not hearing anything about a gallop. Certainly in this terminal stage the patient should have had a gallop, and I would not be surprised if told that he had a pericardial friction rub during the last few days of life.

Certainly the two commonest types of renal lesions we have to consider are either chronic vascular nephritis or malignant hypertension and chronic glomerulonephritis with terminal renal insufficiency. I really do not see any certain way of differentiating these two conditions. Against glomerulonephritis is the fact that we have no history of acute glomerulonephritis or of subacute glomerulonephritis with edema. We have some evidence that the hypertension antedated any knowledge on his part of the urinary abnormalities, and from the level of the blood pressure recorded at entry in the presence of congestive heart failure, one wonders if he had not been carrying a much higher blood pressure during the previous year. This degree of hypertension would certainly be consistent with terminal vascular nephritis. There is nothing in the urinary picture that differentiates the two conditions.

With more renal studies, what other conditions might we encounter? We know that in our diagnoses we must mention chronic pyelonephritis. We have in this case no history of acute infection in the kidneys or a history of renal calculi. There is nothing in the urinary sediment at present that attracts our attention to chronic pyelonephritis. We have a definite statement of fever in the past history but no fever at the time of entry to the hospital. I think we have to discount the possibility of chronic pyelonephritis.

Could this have been an end result of congenital polycystic kidneys? Yes; they may first manifest their presence by the development of hypertension but are certainly far less frequent than malignant hypertension or glomerulonephritis.

Could this renal picture have been due to emboli from the valves of subacute bacterial endocarditis? It could be, but there is no evidence for it. There is no history of fever over a period of time before he came to the hospital and no elevated temperature on admission. There is no statement about any of the other symptoms or ordinary physical signs of subacute bacterial endocarditis. On the other hand, we will not be surprised if Dr. Mallory tells us that the patient had a terminal acute endocarditis.

Could this possibly have been a renal complication of lupus erythematosus? There is no evidence in the past to suggest lupus erythematosus, such as skin lesions, joint symptoms and leukopenia. Could this have been periarteritis nodosa? Again, the absence of fever in the history and the

absence of palpable arterial nodules and eosinophilia at the time of entry make me believe that there is nothing to substantiate that diagnosis. It is merely interesting to mention in passing.

I am going to conclude with a diagnosis of rheumatic heart disease, mitral regurgitation, congestive heart failure, malignant hypertension, chronic vascular nephritis and uremia.

A PHYSICIAN: May I ask whether the phosphatase determination was acid or alkaline?

DR. JACOBSON: Undoubtedly it was alkaline phosphatase. The normal value for alkaline phosphatase is 2 to 5 Bodansky units. I suppose it is routine to ask for serum calcium, phosphorus and phosphatase in patients with renal failure. Is that not so, Dr. Aub?

DR. AUB: Yes; I might say that I have never seen such a marked Chvostek sign in a uremic patient. He did not have such a very marked drop in calcium when allowance is made for the low plasma protein. Yet it was one of the most marked Chvostek signs that I have ever seen. I do not believe that it could have been due to low blood calcium but to the mechanical irritability that comes with uremia. There was one other sign not mentioned — when the patient was lying down the left upper lobe was full of rales and very congested; when he sat up, they all vanished.

DR. TRACY B. MALLORY: Is there any comment on the acute pulmonary edema following intravenous therapy with glucose?

DR. AUB: In my note I said that it was dangerous to give it, but the only chance of survival was to make him urinate. I also recommended fluid, knowing that he might get pulmonary edema and thinking it was worth the risk.

A PHYSICIAN: How much fluid was given?

DR. AUB: Not an enormous amount. He was given 1500 cc. of 5 per cent dextrose in water.

DR. JACOBSON: It may not be amiss at this point to comment to the effect that I had considered the possibility of lower-nephron nephrosis, such as sulfonamide sensitivity, but in view of the complete absence of such a history I did not discuss it.

A PHYSICIAN: In the face of congestion is it good therapy to give a man of that age intravenous fluids?

DR. AUB: I thought it was. It was the only thing we could do for him.

A PHYSICIAN: Would you not use a more concentrated solution instead of so much water if you were trying to bring about diuresis?

DR. AUB: You can have your choice. The patient was going to die anyhow.

CLINICAL DIAGNOSIS

Subacute glomerulonephritis?
Malignant vascular nephritis?

DR. JACOBSON'S DIAGNOSES

Rheumatic heart disease.
Mitral regurgitation.
Congestive heart failure.
Malignant hypertension.
Chronic vascular nephritis.
Uremia.

ANATOMICAL DIAGNOSES

Subacute glomerulonephritis.
Cardiac hypertrophy and dilatation, hypertensive type.
Pulmonary edema, severe.
Bronchopneumonia, slight.
Hydrothorax, bilateral, slight.

PATHOLOGICAL DISCUSSION

DR. MALLORY: I think the autopsy showed conclusively that the patient was going to die, as Dr. Aub has said. I rather expected to find very contracted kidneys after reading through the record. At autopsy we found the kidneys to be larger than normal, weighing 450 gm. (he was not a large man). They were very pale gray, with yellowish mottling, and the gross diagnosis was subacute glomerulonephritis; that was borne out by the microscopical examination. The other findings at autopsy were a very severe grade of pulmonary edema. The lungs weighed a little over 2000 gm., were very distended and failed to collapse when the thoracic cavity was opened. There was very little pleural fluid — 150 cc. on each side. Microscopically we found evidence of incipient pneumonia, but the major portions of the lung showed edema rather than infection. The heart did show recognized scars of previous rheumatic infection. The posterior leaflet of the mitral valve was distinctly shrunken, and the circumference of the valve was only 8.5 mm. whereas the normal is considered 10 to 10.5 mm. There was a slight degree of mitral stenosis and a more significant degree of mitral regurgitation. The heart weighed 450 gm. and the hypertrophy was about equally distributed on the right and left sides, so that I think the hypertrophy was secondary to hypertension as well as to the rheumatic valvulitis. The parathyroid glands were dissected and were not enlarged. Microscopically, however, the fat, which is normally present within the parathyroid gland, had disappeared entirely, indicating slight hyperplasia.

DR. JACOBSON: Do you think that this was subacute bacterial endocarditis arising independently of the antecedent hypertension?

DR. MALLORY: No; I think that the hypertension was probably due to the glomerulonephritis. I would have to admit that this was a slow and silent progression of glomerulonephritis, but one sees cases of this type on occasion.

DR. JACOBSON: Was there any pericardial effusion?

DR. MALLORY: No; we found petechiae on many of the serous surfaces similar to those noted in the skin but no pericarditis, and there was no gastritis or colitis as there frequently is in the uremic state.

DR. AUB: Is there any reason for the bizarre clinical findings in the lungs?

DR. MALLORY: No; I think the immediate mechanism of death was probably pulmonary edema. The intravenous fluid had been given a full two days before death, however, and the pulmonary edema temporarily cleared, only to recur.

CASE 34332

PRESENTATION OF CASE

A sixty-eight-year-old woman entered the hospital complaining of easy fatigability.

About two months prior to admission the patient began to experience progressive weakness and easy fatigability. During this time she had been seen by two physicians, who had been unable to help her. A few hours before admission she developed a severe, steady pain in the right upper quadrant, not affected by breathing or by change in position, and lasting only a few hours. She had not noticed any jaundice, itching or changes in the urine or stools, and had not known of any weight loss.

At the age of thirty-eight she had undergone an apparently normal menopause.

Physical examination revealed a tired, weak, slightly jaundiced woman. A Grade II pulmonary diastolic murmur was heard. A tender, smooth, firm mass was palpated in the left upper quadrant. The edge was not well defined. The mass did not move with respiration and seemed to be medial to the spleen. There was slight erosion of the anterior lip of the cervix.

The temperature was 99.5°F., the pulse 105, and the respirations 24. The blood pressure was 125 systolic, 65 diastolic.

Examination of the blood revealed a red-cell count of 4,200,000, with 15 gm. of hemoglobin, and a white-cell count of 11,700, with 79 per cent neutrophils, 13 per cent lymphocytes and 8 per cent monocytes. Examination of the urine showed a specific gravity of 1.020, a +++ test for albumin, acetone and bile, and a green color with a precipitate on sugar test. The serum nonprotein nitrogen was 41 mg., the total protein 5.9 gm., the cholesterol 610 mg. and the cholesterol esters 125 mg. per 100 cc. The fasting blood sugar was 100 mg., and the alkaline phosphatase 41.8 mg. per 100 cc. A van den Bergh test was 6.4 mg. per 100 cc. direct and 8.2 mg. total. The prothrombin time was 18 seconds (control, 19 seconds). The cephalin-flocculation test was + in twenty-four and forty-eight hours. A catheterized specimen of urine revealed rare colon bacilli and a few nonhemolytic streptococci.

An x-ray film of the chest disclosed no abnormality of the bony thorax. There was some calcification in the right and left first interspaces. The right leaf of the diaphragm was quite high, obscuring the right lower-lung field. There were some linear areas of increased density. The left lung field was not remarkable. The heart appeared enlarged in the region of the left ventricle. A barium enema, with the patient unsatisfactorily prepared, showed no evidence of gross obstruction or gross filling defect in the large colon. A gastrointestinal series showed no esophageal varices. The stomach was displaced to the left and posteriorly by a greatly enlarged liver. No other masses could be made out though there was bulging in the left flank, possibly due to a mass other than the liver. There was flattening along the superior aspect of the proximal duodenum. On the second hospital day a biopsy of the cervix and a vaginal smear were done and both were reported negative.

On the eighth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. JAMES H. TOWNSEND: I would be interested to know whether the pain in the right upper quadrant lasted four hours, twelve hours or twenty-four hours. I take it it was the development of this pain, which she had not had before, that brought about the emergency situation that necessitated the patient's entry into the hospital. I should like to know whether the pain lasted for just a few hours before she came into the hospital, and then disappeared before she was seen, or whether, when she came in, the pain required morphine to relieve it. We are not given any information about that as yet. She had not noticed any jaundice, itching or changes in the urine or stools, and she had not known of any weight loss.

At physical examination on admission she was very jaundiced when first seen — I assume only a few hours after the pain developed. I think that is of importance.

The murmur I assume to have been an early diastolic murmur heard in the second left interspace. There was a wide pulse pressure that may have had significance in relation to the murmur.

Examination of the blood was essentially negative, with the white-cell count slightly on the high side, but no anemia.

Let us pause a moment. This patient had bile in the urine. She had acetone, which suggests that she had not been eating well or had been vomiting. She had albumin, which frequently accompanies bile and suggests that perhaps there had been bile there for some time. The green color on Benedict test, which is a frequent finding with

bile, is not necessarily due to sugar, but may be due to some other substance.

The cholesterol esters were at about a normal absolute level, but the proportion was quite low in relation to the total. The phosphatase was high, and the van den Bergh within middle range. At no point are we told whether there were any cellular elements in the urine — white cells, red cells and so forth.

Presumably the linear areas of increased density described in the x-ray findings were caused by atelectasis associated with the high diaphragm. By x-ray interpretation the liver was greatly enlarged. We are not told on physical examination that the liver edge could be felt in the usual place. May we see the x-ray films at this point?

Dr. Joseph Hanelin: The chest film shows the elevated right leaf of the diaphragm, with a slight amount of linear streaking above it, probably representing atelectasis. The heart is probably enlarged somewhat although it is difficult to be certain of the exact size because the elevated diaphragm may increase the transverse diameter. The lungs otherwise are clear. This film includes the major portion of the abdomen and the barium-filled stomach, which is displaced to the left, presumably by the enlarged liver.

Dr. Townsend: Can you see the lower border of the liver?

Dr. Hanelin: I would assume that it was opposite the third lumbar vertebra.

Dr. Townsend: It is covered by gas so that you cannot define the lower edge too well as to position or exact shape.

Dr. Hanelin: That is right. We do not see the lower contour. The stomach is displaced somewhat to the left, and in the lateral projection the stomach is displaced posteriorly.

Dr. Townsend: In the lateral view can you see where the liver is?

Dr. Hanelin: I cannot definitely outline it.

Dr. Townsend: The liver is not sufficiently enlarged to push the hepatic flexure into the pelvis, is it?

Dr. Hanelin: No.

Dr. Townsend: Most of the liver is above the iliac crest?

Dr. Hanelin: Yes.

Dr. Townsend: There are one or two simple laboratory observations that we are not given. I wonder if they were done. We are given a good many blood chemical findings, but we are not told anything about the character of the stools, either the gross appearance or chemical reactions.

Dr. Tracy B. Mallory: The stools were brown and guaiac negative. The urine contained a few pus cells, but the number was not estimated.

Dr. Townsend: But no chemical test was done on the stool for bile pigment or urobilinogen? Was there a test for urobilinogen in the urine? Evidently not.

We have, then, an elderly woman, with a two months' history of failing health, who had pain only a few hours before admission and at the time of admission was already clinically jaundiced. I am curious to know on which day the van den Bergh test was done; was that observation almost immediately after she came in or after the passage of some days?

Dr. Mallory: The test was made on the day after entry.

Dr. Townsend: She had a reasonably high van den Bergh reaction, which I do not believe developed in the twenty-four hours since she began to have pain. In other words, I believe she had jaundice before she had pain, and this has a different significance from jaundice appearing some days after pain.

The important features of the physical examination are jaundice, an abdominal mass and a diastolic murmur. The blood showed no anemia. We have many of the usual battery of tests done in an attempt to establish the cause of jaundice. In general, we divide these tests into those that point toward obstruction of the extrahepatic biliary passage and those that point toward disturbance of intrahepatic cellular function. Rarely do we get a clear-cut picture. The findings are usually mixed. In this case the high alkaline phosphatase and the high total cholesterol are strongly in favor of external obstruction (probably complete obstruction at these levels), although we would like very much to know whether there was complete obstruction demonstrated by the absence of bile pigment in the stools and the absence of urobilinogen in the urine. However, we do not have that information. The van den Bergh reaction is consistent with complete external obstruction. The slightly low total protein, on the other hand, the relatively low cholesterol esters and the + cephalin-flocculation test point toward damaged liver parenchyma. It was not damaged enough, however, to influence the prothrombin time, which in this case was normal.

The patient was operated on. We have to estimate what was most likely to be found at that operation. Let us look at it from the point of view of the mass described in the left upper quadrant. It was smooth, ill defined and tender. What masses of this sort occur in the left upper quadrant? The kidney is in that region. We have little information about the kidney. At least, there was no blood or pus coming from it. I assume that no intravenous pyelogram was done, or we would have been given that information. On the x-ray films I do not believe that we can see the kidney, and it was not described in the physical examination as a kidney mass would have been. Before examination at the hospital it was thought that it was definitely

not the spleen, and I do not believe that it was the spleen. Could it have been part of the larger mass that the roentgenologists thought might be liver? Yes; the left lobe of the liver might present such a mass, particularly if it was involved with metastatic disease, and that is a definite possibility.

What else could this mass have been? It could obviously have arisen in the pancreas, which is in that region; and pancreatic masses either solid or cystic type, benign or malignant, can present such a mass. They are usually not described as tender. However, I am sure I have seen cases of carcinoma of the pancreas that developed a large, tender mass before the patient died.

If this mass represented a metastasis in the left lobe of the liver, would it have been tender? Usually metastatic masses are not tender, and they are usually not painful. I think it is possible for such a mass to become tender if it is infarcted or has had a hemorrhage in it. I still think that this could have been the left lobe of the liver and that it could have been tender.

Our tests do not give us absolute proof as to whether we are dealing with a straight case of external obstruction or with damage to the liver parenchyma. They suggest a combination. I think that we have to look at the picture as a whole and consider the most probable diagnosis. I gather from the x-ray films that the liver was not tremendously large.

One can say almost with certainty that a liver of this size in a person of this age comes from metastatic carcinoma. The only other condition that frequently causes these very large livers at this age is leukemia, and that I think is ruled out by the blood picture. What was the probable source? We can pretty well rule out the colon. The patient had a pelvic examination, and although not specifically mentioned, I assume that no masses were felt. Probably these metastases did not arise from the pelvic organs, although that is a common source. A small tumor in the ovary can lead to tremendous metastases in the liver. It was apparently not in the stomach. I think it would have been seen if it had been in the stomach, although we all know that a tiny carcinoma in some part of the stomach may not be seen on x-ray study. But I think it is a very distant possibility when painless jaundice comes on at this age. I speak of this as painless jaundice because she was already jaundiced when she was first seen, and there was not time to develop that degree of jaundice after the pain began. The tumor that causes such a situation usually originates either in the pancreas or in the bile duct. I do not believe that it is possible clinically to differentiate the two. Such livers can also come from metastases from a lung tumor, but from what we can see of the lungs there appears to be no primary source in the nature of a bronchiogenic carcinoma. It is not necessary that the original tumor should have blocked the bile duct. Sometimes metastases themselves, in lymph nodes in the region of the bile duct, can cause such obstruction. I am assuming it was complete obstruction because of the finding of a very high alkaline phosphatase and high total cholesterol. However, the observation of brown stools suggests that it was not complete obstruction; that is a single finding and we cannot rely on it without more chemical tests.

Could this woman possibly have had the one condition that leads to external obstruction and that is amenable to surgery — a stone in the common duct? The possibility is very remote because she had been going downhill and feeling generally weak for two months before the onset of pain and because she was jaundiced when first seen within a few hours after the onset of pain.

I shall, therefore, conclude by saying that the probability is that this woman had metastatic disease, presumably carcinoma, in the liver, probably arising from the pancreas, possibly the bile duct, and also possibly from some other source that I have mentioned. I do not believe that cirrhosis of the liver could produce such a picture. One almost never sees such a high cholesterol in cirrhosis of the liver. One can get pain like this in cirrhosis. Can it be a primary tumor in the liver? These are rare tumors usually arising in persons who already have had cirrhosis, of which we have no evidence here, whereas there is considerable evidence that she did not have cirrhosis. She had no esophageal varices. She did have a very high total cholesterol and no change in the prothrombin time. I therefore expect that whatever operation was done — whether it was an exploration, a punch biopsy or a peritoneoscopy — showed metastatic disease in the liver. As a probable source I should think that the pancreas was most likely. The painful mass may have been either the left lobe of the liver or the pancreas.

DR. PERRY CULVER: I saw this woman with the third-year students. We were impressed with the severity of the patient's illness, and we were primarily concerned with the epigastric mass. We could not feel the liver at this examination, but in the Out-Patient Department the mass seemed to us to represent cancer of some sort. We thought that it was probably metastatic neoplasm. We admitted the patient to the house immediately as an emergency. That is as far as we went with the diagnosis at that time.

I should also like to say that we usually disregard a + cephalin-flocculation test as being within normal limits.

DR. TOWNSEND: I agree.

DR. CULVER: Another interesting point is that there is an occasional rare case with brown stools that, on repeated examinations, are completely devoid of bile pigment. Schiff* has reported this same observation.

CLINICAL DIAGNOSES

Metastatic carcinoma of liver.
Uremia.

DR. TOWNSEND'S DIAGNOSIS

Metastatic carcinoma of liver (probable primary source in pancreas or bile duct).

ANATOMICAL DIAGNOSES

Carcinoma of gall bladder, with massive involvement of liver and metastases to adrenal glands.
Pulmonary congestion and edema.
Cholelithiasis.
Pulmonary tuberculosis, old.

PATHOLOGICAL DISCUSSION

DR. MALLORY: The operation mentioned was a peritoneoscopy. There had been considerable discussion as to whether or not exploratory laparotomy or peritoneoscopy should be performed. Oddly enough it was the surgeons who did not wish to explore the patient and urged the peritoneoscopy. The liver was studded with tumor nodules. The patient went rapidly downhill and died without any symptoms of note. At autopsy we found that almost all the liver tissue had been replaced by tumor. In cross-section the largest mass of this tumor was centered around the gall-bladder area, and in the gall bladder was a small papillary tumor, which we believed to be the primary site, with direct lymphatic spread throughout the liver substance. There were very few metastases in the body — two small ones in each adrenal gland and one small metastasis in the bone marrow, found more or less by accident in our microscopical sections. There were no metastases to the lung. The gall bladder contained numerous stones, and we also found three small stones in the common duct, which, however, was not dilated.

DR. TOWNSEND: I meant to say that sometimes patients have both carcinoma and gallstones and that perhaps the pain at the time she came in was due to gallstones but I did not believe that stones caused the whole picture.

DR. MALLORY: Cancer of the gall bladder almost never occurs in the absence of cholelithiasis.

DR. TOWNSEND: Was the large mass felt on the left side caused by metastases in the left lobe of the liver?

DR. ROY V. BUTTLES: I could not be sure that the mass felt on the left side was the lobe of the liver. It did not seem to be particularly enlarged.

DR. TOWNSEND: There was nothing else external to the liver or behind the liver?

DR. MALLORY: No.

DR. JAMES HEIL: May I ask about the pulmonary diastolic murmur?

DR. TOWNSEND: I meant to comment on that also. She may have had old rheumatic heart disease. I assume that a blood Hinton test was done, but I doubt very much the likelihood of a syphilitic process. She may have had sclerotic changes in the aortic valve, which could produce such a murmur in a patient of this age — probably calcific aortic valve disease, not marked.

DR. MALLORY: We did not find anything to explain the murmur. The heart was entirely normal.

*Schiff, L. *Differential Diagnosis of Jaundice.* 313 pp. Chicago: Year Book Publishers, Incorporated, 1946. P. 230.

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MEDICAL EXPERTS ON THE ATOMIC AGE

THE world terror characterizing the dawn of the Atomic Age seems at first glance to be something new and unique in human affairs. In a mood of incredulous despair the thoughtful people of the western world stand appalled at the magnitude of the danger. In quite a different mood, scientific experts are now beginning to preach a hard-headed gospel of preparedness. If our courage falters at the earnestness of their words it may be well for us to draw strength from a backward glance to another time when civilization found itself also in an evil case.

It was in the spring of 1242, eighteen years after the mysterious Mongol horde of Genghis Khan had irrupted into eastern Europe to massacre a Christian army at the Kalka river; thirteen years after the dreaded horse archers had turned back to lay waste northern China while Europe shuddered through an uneasy lull; and three years after the Asiatic terror had again loomed across the Russian steppes.

These last three years had seen eastern Europe suffer the most fearful disasters — far worse than anything Attila and his Huns had brought. "The Mongols," according to Oman* "represented not mere conquest but blind and wilful destruction; they left deserts behind them where there had been a civilized and thickly peopled group of states and killed for killing's sake." The armored chivalry of Christendom — the best that Europe could produce — melted before them. Nations in their path forgot their local quarrels and united, but too late. Now led by Batu Khan, the horde trampled down Russia, Poland and Silesia. On April 5, 1241, they had annihilated an allied army of Germans, Moravians and Poles at Liegnitz and then had rapidly overrun the Balkan peninsula. Now indeed "a shock of terror went round the whole of Christendom." The last barrier was down, and with the approach of spring Batu Khan stood at the unprotected German border. Doubtless the unheeded warning of the River Kalka and the far-off fate of China were then remembered, and the thirteen wasted years of the "cold war" regretted. Western Europe saw its "atomic age" close at hand, and it was appalled.

But then, as now, there were experts to substitute reasoned action for despair. Observing siegecraft to be the weak side of Mongol tactics, military engineers advised building strong fortresses and castles — the people built them. Advised to unite for common defense, the nations united and braced themselves for inevitable disaster, but disaster never came. Batu Khan, after breaking his teeth on the first strongly fortified and defended cities suddenly faded into the east, and Western Europe, after a year of intense terror, finding itself inexplicably freed from all danger, was able to resume its endless local wars.

On August 6, 1945, a detonation over Hiroshima announced the advent of our own Atomic Age. Again the shock of terror, which is not new, is

*Oman, C. *A History of the Art of War in the Middle Ages*. Second edition. 2 vol. London: Constable & Co., 1924.

being felt round the world. And again the experts are speaking.

Colonel Wesley C. Cox and Major A. J. Bauer, Army Medical Corps, experts from the Surgeon General's Office, discussed "Military Epidemiology and Preventive Medicine in the Atomic Age" at the Harvard School of Public Health on May 26, 1948. Their remarks dealt with two aspects of the problem of preparedness: the immediate implications of an atomic bomb attack within the next five years; and the broader implications of producing a civilization capable of surviving the consequences of atomic bomb attacks in a more remote future.

They began by pointing out the enormous shocking power of the latest explosives, and the magnitude of the devastation one bomb can cause. Between 15,000 and 200,000 casualties can be expected in a city of 1,000,000 population. All the measures now taken in cases of widespread disaster will be needed, but on a vastly larger scale. Tremendous supplies of drugs, dressings and other medical equipment will be required. Blood transfusions will be used in fantastic numbers. Treatment of initial injuries will involve rescue, evacuation, sorting, nursing care, antibacterials, vitamin C, intravenous administration of fluids and blood and the surgery of trauma and burns. Later treatment of survivors may be directed to the effects of radiation illness, the radiation damage being evaluated by frequent lymphocyte counts. Agents of questionable value such as vitamin B_6, toluidine blue, protamine sulfate, rutin and adrenocortical hormones may be used. "Of first importance following the rescue and first-aid ministrations to those known to have been exposed to excessive radioactivity is the administration of drugs to prevent the development of capillary and vascular fragility." Many laymen will have to be taught the technic of blood grouping, transfusion, cell counts and other medical skills to supplement the efforts of the physicians. Each community will have to organize a "civil-defense task-team" made up of experts in several fields as well as a civilian-defense force based on the experience of the English in World War II. A grim note is sounded by the statement that "the director of the emergency plan for one city must be a resident in some other community." Shelters, potable water, waste disposal, food spoilage both by irradiation and by electric power disruption, detection and control of epidemics must also be envisioned. "The power of this weapon is so great that . . . we cannot afford not to plan as long as any possibility of attack is present."

Colonel Cox and Major Bauer then spoke of the long-range plans that may be necessary if humanity is to survive in the Atomic Era:

> The advent of the Atomic Period has oriented us to new concepts and wider horizons. We have adopted a broader view of democracy and fully recognize that although we are in a time of technocracy we have also entered into an era of renewed interest in the individual.

This leads them to discuss such apparently diverse subjects as trends in medical education, means of extending the span of economic usefulness in an aging population, the elimination of chronic diseases, eugenics, maternal health, periodic health examinations, prevention of dental caries, child psychology as an approach to reducing later neuropsychiatric instability, dietetics, and many others. "Only through such comprehensive National programs . . . may we envision the development during the future Atomic Era of a physically strong well-developed population, psychologically and mentally well conditioned and hardened and free of the preventable defects, disabilities and diseases which have so long plagued us."

Major Bauer ended with a thought that must surely have entered the minds of the thirteenth-century military experts while they were pushing their fortifications to completion:

> The most important preventive measure in preparation for an atomic bomb attack is outside of our field. That is a national policy which will make all of our efforts superfluous.

STREPTOMYCIN RESISTANCE OF TUBERCLE BACILLI

It is now well known that the development of resistance of the infecting organism is one of the most important limiting factors and the greatest cause of failures of streptomycin in the treatment of tuberculosis. Two recent studies shed further light on certain aspects of this phenomenon.

Sadusk and Swift[1] tested the in vitro streptomycin sensitivity of tubercle bacilli isolated from sputum or gastric washings at monthly intervals in a group of 16 patients with pulmonary tuberculosis receiving 1.8 gm. of streptomycin daily for a period of four months. In these cases 14 of the strains of bacilli isolated before treatment were sensitive to 0.5 microgm. of streptomycin per cubic centimeter of the culture medium used, and 2 were sensitive to 1.0 microgm. Loss of sensitivity of the organisms, as evidenced by at least tenfold increase in resistance, began to appear by the end of the first month of therapy at a time when conversion of positive sputum or gastric washings to negative was observed in cultures of other cases. By the end of the third and fourth months of therapy 9 patients still had positive cultures; in 5 the organisms had increased tenfold to fiftyfold in resistance, and the remaining strains increased from one hundredfold to more than two thousandfold in resistance. There was no clear-cut correlation between resistance to streptomycin and the clinical course of these patients under therapy.

Another more detailed and somewhat more illuminating study was reported a few months previously by Pyle,[2] who made direct quantitative studies of the sputum of 8 patients with far advanced tuberculosis who were raising large amounts of sputum that was loaded with tubercle bacilli. These people were treated with streptomycin continuously with a dosage of 0.25 gm. every six hours for four or five months. In each case the sediment from a twenty-four-hour specimen of sputum was concentrated to determine the total number of organisms present. The specimen was cultured on plates containing graded concentrations of streptomycin, and the number of organisms growing without the streptomycin and in varying concentrations of the agent was determined. This was repeated at weekly intervals throughout the course of treatment.

In 7 of the 8 cases a few relatively resistant organisms were found in the cultures of the sputum obtained before streptomycin was started. In each of these cases from four to forty-two colonies grew on plates of mediums containing 5 microgm.; from one to eight colonies grew in 10 microgm. of streptomycin per cubic centimeter, and no colonies grew on mediums containing 25 or more microgm. per cubic centimeter before treatment was started. The total bacterial count in the same amount of inoculum in 2 cases was in the vicinity of 100,000 and 350,000.

It was evident from these pretreatment studies that any large population of tubercle bacilli could be expected to contain organisms that are relatively resistant to streptomycin without having previously been exposed to the drug. In all 8 cases, however, the predominant strains of *Mycobacterium tuberculosis* were sensitive to from 0.6 to 1.25 microgm.

In 4 of the 8 cases the originally predominantly sensitive strains of tubercle bacilli were replaced during therapy by strains that were predominantly resistant to 1000 or more micrograms of streptomycin per cubic centimeter. In an additional case the strain became sensitive to 50 microgm. at the end of eight weeks; in 2 cases the strains retained their original sensitivity throughout, and in the final case only a minimal degree of resistance occurred at the end of four and a half months of treatment.

In the 4 cases in which resistance developed, the weekly cultures showed a more or less gradual increase in the number of resistant organisms and in the degree of resistance to streptomycin. This increase began within one to four weeks after treatment was begun, although the strains were not predominantly resistant until from six to thirteen weeks. For example, at the time when a number of colonies grew in medium containing as much as 100 microgm. of streptomycin per cubic centimeter the vast majority of the bacterial population was still quite sensitive to streptomycin and the patients presumably could be expected to continue to receive benefit from chemotherapy.

From a practical point of view these findings suggest that most of the benefits that take place from streptomycin treatment in the majority of cases of tuberculosis will be obtained during the first month of treatment, and thereafter the effects of therapy decline so that probably no benefit is obtained after the end of two or three months. This is true, at least in the cases in which a sensitive flora is

replaced by a predominantly resistant one during the course of treatment.

References

1. Sadusk, J. F., Jr., and Swift, W. E., Jr. Sensitivity of tubercle bacillus to streptomycin before and during specific therapy. *J. Clin. Investigation* **27**:278-282, 1948.
2. Pyle, M. M. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. *Proc. Staff Meet. Mayo Clin.* **22**:465-473, 1947.

TERATCGENETIC AND LETHAL EFFECTS OF EMBRYONIC INFECTIONS

The recent observations on the occurrence of congenital defects in the offspring of mothers who have had rubella during pregnancy have stimulated interest in the whole subject of intrauterine or embryonic infections and of all types of infections and illnesses in the mother during pregnancy. An interesting experimental approach to this subject was made by Hamburger and Habel.* For their studies they used infections with influenza A and mumps virus in the developing hen's eggs.

The chick embryo suggested itself as a suitable embryonic material since it is known that the tissues of the extraembryonic membranes of the chick embryo are a favorable medium for the culturing of a number of viruses. Furthermore, the absence of a placenta in the developing chick makes a direct infection of the embryo possible, thus avoiding the complications introduced by an extraembryonic barrier.

The experimental evidence produced from these studies showed that the influenza A virus has teratogenetic effects on the early chick embryo. It produced a specific syndrome comprising microcephaly and micrencephaly, twist of the axis and impairment of the growth of the amnion. Furthermore, the virus was lethal for early embryos within three days of infection. The mumps virus was likewise lethal for early embryos five days after infection; it did not produce specific abnormalities, but seemed to raise the incidence of malformations of the types that occasionally occur in uninfected chick embryos.

The authors believe that their results place influenza A virus in a line with the rubella virus as a teratogenetic agent. Their observations on influenza A infections in chick embryos also confirmed those on rubella in human beings in that only infections of early embryos resulted in abnormalities. Chick embryos of four days' incubation were killed by the influenza virus, but it seemed that in that stage of development most organs have passed the critical period at which their morphogenesis could be directed into atypical channels.

Their findings were also of interest in that the patterns of infectiousness were different for the embryo and for the fully developed structures. In the embryo the brain tissues seemed to be particularly susceptible to influenza A virus, whereas in the adult the respiratory mucous membranes were primarily affected. In mumps the infection of the salivary glands is not infrequently combined with meninigitis, but no effect on the brain was found macroscopically in embryos. Hamburger and Habel regarded the situation with mumps in chick embryos as the same as that in rubella during pregnancy, in which the embryonic defects seem to have no obvious relation to the manifestations of rubella infections in older phases of life.

*Hamburger, V., and Habel, K. Teratogenetic and lethal effects of influenza-A and mumps viruses on early chick embryos. *Proc. Soc. Exper. Biol. & Med.* **66**:608-617, 1947

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

REIMBURSEMERNT FOR HOSPITAL CARE

Reimbursement for the hospital care of a patient with venereal disease who cannot afford to pay for hospitalization has been increased from $4.50 to $6.50 per diem, in accordance with Chapter 669 of the Acts of 1948, the Massachusetts Department of Public Health announces. This increased rate, which became effective on July 1, 1948, shall constitute reimbursement in full for all services rendered the patient.

MISCELLANY

NEW YORK UNIVERSITY HEALTH-EDUCATION INSTITUTES

A series of annual health-education institutes is to be held at New York University under the sponsorship of the School of Education. The first of these institutes to be held this summer from August 16 to September 3, 1948, under the Department of Physical Education and Health, School of Education, in co-operation with the American Association for the Advancement of Science, the Research Council on Problems of Alcohol and other national agencies, will be devoted to problems in alcohol education.

CORRESPONDENCE

BOARD OF REGISTRATION IN MEDICINE

To the Editor: At the annual meeting of the Board of Registration in Medicine held July 13, the following officers were elected for the ensuing year: George L. Schadt, M.D., Springfield, secretary, and Gordon M. Morrison, M.D., Boston, chairman.

The other members of the Board are as follows: Anthony O. Cardullo, M.D., Boston; Robert C. Cochrane, M.D., Boston; Charles E. Donovan, D.O., Salem; Roger T. Doyle, M.D., Boston; and Bancroft C. Wheeler, M.D., Worcester.

GEORGE L. SCHADT, M.D. *Secretary*
Board of Registration in Medicine

State House
Boston

STATISTICALLY SPEAKING

To the Editor: I should like to call attention to the following facts in reference to the article, "Swimming Pools: Their relation to illness," by Dr. J. Roswell Gallagher, which appeared in the June 24 issue of the *Journal*:

Upon examination of the statistics presented in Table 1 of the article, one finds that the average number of hospital admissions for swimmers (0.354) is wrong. This average was obtained by adding the hospital admissions per swimmer (0.770 plus 0.290 and so forth) and dividing by 7. This is an unweighted average, since it does not take into account the number of swimmers in each year. The correct, weighted average is obtained by dividing the total number of hospital admissions (of swimmers) by the total number of swimmers. I have calculated these values and found that the total number of admissions (269) divided by the total number of swimmers (815) gives the *true* average of 0.330 hospital admissions per swimmer. Similarly, the figures for nonswimmers were calculated and the total number of admissions (1068) divided by the total number of swimmers (3500). Curiously enough, this weighted average equals the unweighted average of 0.305.

The percentage increase of admissions of swimmers over nonswimmers is now only 7.5 per cent. Upon closer statistical analysis of this figure it turns out that the standard deviation of the difference of the averages is 0.018. Since the difference of the average (0.330 minus 0.305) is only 0.025, the deviation from zero or [0.025-0/0.018 is 1.4 sigma. This means that the figure 7.5 per cent is statistically not significant. Thus the difference between swimmers and nonswimmers could easily occur by chance alone.

Since reference to Dr. Gallagher's article was made in the current issue of *Time* without Dr. Gallagher's cautious reservations regarding the validity of the figure 14 per cent, and since exact evaluation of the data yields only 7.5 per cent with a deviation of 1.4 sigma, making this figure without statistical significance, I believe that these findings should be brought to the attention of the editors of *Time* so that the lay population may not be misled. The readers of the *New England Journal of Medicine* might also be interested in these findings.

HANS W. NEUBERG, '50
College of Physicians and Surgeons
Columbia University

Mr. Neuberg's letter was referred to Dr. Gallagher, whose comment is as follows:

To the Editor: This is a valid comment. Through an oversight the raw data in Table 1 were not reduced to a "per boy" basis, the method that was used in the other similar tables in this paper. The discussion and summary, however, made it clear that the differences in illness were slight.

J. ROSWELL GALLAGHER, M.D.

NOTICES

ANNOUNCEMENT

Dr. Thomas B. Quigley announces the removal of his office to 319 Longwood Avenue, Boston.

WANTED BY THE FBI

Hugo Bob Hubsch, with aliases of Robert C. Glass, R. C. Harris, Hogo Hobsch and Louis S. Miller, is being sought by the Federal Bureau of Investigation. On November 7, 1945, a Federal Grand Jury at Jackson, Mississippi, returned an indictment charging this man with a violation of the National Stolen Property Act. He is charged with another violation of the National Stolen Property Act in a complaint filed with a United States Commissioner at Birmingham, Alabama, on June 7, 1948. This man has defrauded numerous physicians and hospitals in the Eastern and Southeastern sections of the United States during the past few months through the medium of fraudulent checks.

Investigation has revealed that Hubsch has a chronic kidney ailment, and it has recently been ascertained that he has a large kidney stone in the right ureter about 10 cm. below the kidney. This condition has caused local inflammation, which, at varying intervals, results in almost unbearable pain. He has been advised that it will be necessary for him to undergo major surgery for the removal of the stone in the near future, and until that surgery is performed he will need frequent, if not continuous medical attention. This fugitive moves about rapidly in the section of the United States east of the Mississippi River, and he has recently given numerous physicians and hospitals fraudulent checks in return for treatment, hospitalization, sedatives and narcotic prescriptions.

The following is a composite description of Hugo Bob Hubsch: age, about fifty-two (claims to have been born in Budapest, Hungary, on November 4, 1895); height, about 5 feet, 6 inches; weight, 140 to 170 pounds; hair, dark brown, graying; eyes, brown; build, medium; race, white; nationality, believed to be naturalized American; occupations, laborer, pharmacist; scars and marks, left arm partially paralyzed, needle scars on both arms, large scars above each hip resulting from kidney operations, shrapnel scars and two bullet scars on abdomen, bridge in upper front teeth; characteristics, long nose, stooped posture.

Anyone having information concerning the whereabouts of this fugitive should immediately notify the nearest office of the Federal Bureau of Investigation or the local law-enforcement agency.

ANNUAL MEETING OF NATIONAL COMMITTEE FOR MENTAL HYGIENE, INC.

The annual meeting of the National Committee for Mental Hygiene will be held on November 3 and 4 at the Hotel Pennsylvania, New York City. The program will consist of four scientific sessions during the mornings and afternoons, a business luncheon on the first day and the annual luncheon on the second day at which the presentation of the Lasker Award of $1000, presented annually for outstanding service in some field of mental hygiene, will be made and the ten-year national program for mental health discussed.

Further information may be obtained from the National Committee for Mental Hygiene, 1790 Broadway, New York 19, New York.

(*Notices concluded on page xiii*)

NOTICES (*Concluded from page 282*)

AMERICAN CANCER SOCIETY ANNOUNCEMENT OF GRANTS AND FELLOWSHIPS

The Committee on Growth of the National Research Council, acting for the American Cancer Society, is entertaining applications for grants and fellowships. Applications for extension of existing grants in cancer research will be received until October 1, and applications for new grants until November 1. Final decision on applications submitted during this period will be made in most cases soon after February 1. Grants approved at this time ordinarily will become effective July 1, 1949.

Fellowship applications may be submitted at any time. Those received prior to November 1 will be acted upon by the Committee on Growth in December. Those received between November 1 and March 1 will be acted upon in April. Fellowships ordinarily will begin July 1, though this date may be varied at the request of the applicant.

During the past year the American Cancer Society, Inc., on recommendation of the Committee on Growth has approved research grants and fellowships totaling over $2,000,000.

Communications regarding grants and fellowships should be addressed to Executive Secretary, Committee on Growth, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, AUGUST 19

FRIDAY, AUGUST 20

*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

TUESDAY, AUGUST 24

*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.

*1:30–2:30 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

WEDNESDAY, AUGUST 25

*12:00 m.–1:00 p.m. Clinical Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.

*Open to the medical profession.

AUGUST 11–21. International Congress on Mental Health. Page 344, issue of March 4.

AUGUST 23–26. International Society of Hematology. Page 419, issue of March 18.

AUGUST 26–28. American Association of Blood Banks. Page 420, issue of March 18.

SEPTEMBER 7–11. American Congress of Physical Medicine. Page 582, issue of April 15.

SEPTEMBER 7–11. American Occupational Therapy Association. Page xv, issue of July 8.

SEPTEMBER 9. Some of the Advances in Surgery. Dr. Frank H. Lahey. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

SEPTEMBER 13–15. American Academy of Pediatrics. Olympic Hotel. Seattle, Washington.

SEPTEMBER 16–18. Vermont State Medical Society. Annual Meeting. Burlington.

SEPTEMBER 20–23. American Hospital Association. Page 310, issue of February 26.

SEPTEMBER 22. New England Conference of Industrial Physicians and Surgeons. Page 244, issue of August 5.

SEPTEMBER 29. Mississippi Valley Medical Editors' Association. Page 170, issue of January 29.

OCTOBER 6–9. American Board of Ophthalmology. Page 170, issue of January 29.

OCTOBER 18–22. American College of Surgeons. Page 34, issue of July 1.

OCTOBER 27. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

NOVEMBER 1–3. American Clinical and Climatological Association. Page 582, issue of April 15.

NOVEMBER 3 and 4. Annual Meeting of National Committee for Mental Hygiene, Inc. Page 282.

NOVEMBER 8–12. American Public Health Association. Page 420, issue of March 18.

NOVEMBER 10–13. Association of Military Surgeons of the United States. Page 722, issue of May 13.

NOVEMBER 20–23. American Academy of Pediatrics. Annual Meeting. Chalfonte-Haddon Hall Hotel, Atlantic City, New Jersey.

DECEMBER 7–9. Southern Surgical Association. Annual Meeting. Page 543, issue of April 8.

DECEMBER 9 and 10. New York State Society of Anesthesiologists. Page 34, issue of July 1.

FEBRUARY 4, 1949. American Board of Obstetrics and Gynecology, Inc. Page 244, issue of August 5.

MARCH 28–APRIL 1, 1949. American College of Physicians. Page 158, issue of July 22.

NOVEMBER 11–17, 1949. Third Inter-American Congress of Radiology. Page 158, issue of July 22.

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BRIEF HISTORICAL NOTES ON MEAD'S CEREAL, PABLUM AND PABENA

HAND in hand with pediatric progress, the introduction of Mead's Cereal in 1930 marked a new concept in the function of cereals in the child's dietary. For 150 years before that, since the days of "pap" and "panada," there had been no noteworthy improvement in the nutritive quality of cereals for infant feeding. Cereals were fed principally for their carbohydrate content

The formula of Mead's Cereal was designed to supplement the baby's diet in minerals and vitamins, especially iron and thiamine. How well it has succeeded in these functions may be seen from two examples:

(1) As little as one-sixth ounce of Mead's Cereal* supplies over 50% of the iron and 20% of the thiamine minimum requirements of the 3-months-old infant. (2) One-half ounce of Mead's Cereal furnishes all of the iron and 60% of the thiamine minimum requirements of the 6-months-old baby.

That the medical profession has recognized the importance of this contribution is indicated by the fact that cereal is now routinely included in the infant's diet as early as the third or fourth month instead of at the sixth to twelfth month as was the custom only a decade or two ago.

In 1933 Mead Johnson & Company went a step further, improving the Mead's Cereal mixture by a special process of cooking, which rendered it easily tolerated by the infant and at the same time did away with the need for prolonged cereal cooking in the home. The result is Pablum, an original product which offers all of the nutritional qualities of Mead's Cereal, plus the convenience of thorough scientific cooking.

During the last twelve years, these products have been used in a great deal of clinical investigation of various aspects of nutrition, which have been reported in the scientific literature.

Many physicians recognize the pioneer efforts on the part of Mead Johnson & Company by specifying Mead's Cereal and PABLUM—and also the new Pablum-like oatmeal cereal known as PABENA.

*Pablum, the precooked form of Mead's Cereal, has practically the same composition: wheatmeal (farina), oatmeal, cornmeal, wheat embryo, beef bone, brewers yeast, alfalfa leaf, sodium chloride, and reduced iron.